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(54) Title: HETEROCYCLIC MCHr1 ANTAGONISTS AND THEIR USE IN THERAPY

(57) Abstract: Compounds of formula I depicted below, pharmaceutical compositions containing them, processes for preparing the compounds, and their use in the treatment of obesity, type II diabetes, metabolic syndrome, psychiatric disorders, cognitive disorders, memory disorders, schizophrenia, epilepsy and related conditions, neurological disorders such as dementia, multiple sclerosis, Parkinson's disease, Huntington's chorea and Alzheimer's disease, and pain related disorders. The compounds are melanin concentrating hormone receptor 1 (MCHr1) antagonists.

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Heterocyclic MCHr1 antagonists and their use in therapy

Field of invention

The present invention relates to certain compounds of formula I, to processes for preparing such compounds, to their use in the treatment of obesity, psychiatric and neurological disorders, and to pharmaceutical compositions containing them.

Background of the invention

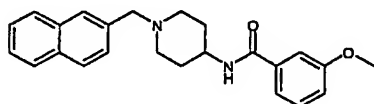
Melanin concentrating hormone (MCH) is a cyclic peptide that was first isolated from fish over 15 years ago. In mammals, MCH gene expression is localised to the ventral aspect of the zona inserta and the lateral hypothalamic area (Breton et al., *Molecular and Cellular Neurosciences*, vol. 4, 271-284 (1993)). The latter region of the brain is associated with the control of behaviours such as eating and drinking, with arousal and with motor activity (Baker, B., *Trends Endocrinol. Metab.* 5: 120-126(1994), vol. 5, No. 3, 120-126 (1994)). Although the biological activity in mammals has not been fully defined, recent work has indicated that MCH promotes eating and weight gain (US 5,849,708). Thus, MCH and its agonists have been proposed as treatments for anorexia nervosa and weight loss due to AIDS, renal disease, or chemotherapy. Similarly, antagonists of MCH can be used as a treatment for obesity and other disorders characterised by compulsive eating and excessive body weight. MCHr1 projections are found throughout the brain, including the spinal cord, an area important in processing nociception, indicates that agents acting through MCHr1, such as compounds of formula I, will be useful in treating pain.

Two receptors for MCH (MCH receptor 1 (MCHr1) (Shimomura et al. *Biochem Biophys Res Commun* 1999 Aug 11;261(3):622-6) & MCH receptor 2 (MCHr2) (Hilol et al. *J Biol Chem.* 2001 Jun 8;276(23):20125-9)) have been identified in humans, while only one (MCHr1) is present in rodent species (Tan et al. *Genomics* 2002 Jun;79(6):785-92). In mice lacking MCHr1, there is no increased feeding response to MCH, and a lean phenotype is seen, suggesting that this receptor is responsible for mediating the feeding effect of MCH (Marsh et al. *Proc. Natl. Acad. Sci. USA*, 2002 Mar 5;99(5):3240-5). In

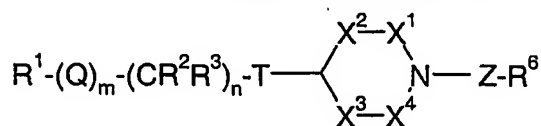
addition, MCHr1 antagonists have been demonstrated to block the feeding effects of MCH (Takekawa et al. *Eur. J. Pharmacol.* 2002 Mar 8;438(3):129-35), and to reduce body weight & adiposity in diet-induced obese rats (Borowsky et al. *Nature Med.* 2002 Aug;8(8):825-30). The conservation of distribution and sequence of MCHr1 suggest a similar role for this receptor in man and rodent species. Hence, MCHr1 antagonists have been proposed as a treatment for obesity and other disorders characterised by excessive eating and body weight.

WO 03/106452 discloses certain 1-substituted-4-(substituted amino)piperidines which are alleged to be MCHr1 antagonists.

An abstract (No. 343 Vu V. Ma et al.,) from the 224th ACS meeting in Boston, MA, USA presents a MCH receptor antagonist for the potential treatment of obesity, with the following structure:



WO 01/14333 discloses that compounds of the following formula:



wherein

Z is CR^4R^5 , $C(O)$ or $CR^4R^5-Z^1$;

Z^1 is C_{1-4} alkylene (such as CH_2), C_{2-4} alkenylene (such as $CH=CH$) or $C(O)NH$;

R^1 represents a C_1 - C_{12} alkyl group optionally substituted by one or more substituents independently selected from cyano, hydroxyl, C_1 - C_6 alkoxy (such as methoxy or ethoxy),

C_1 - C_6 alkylthio (such as methylthio), C_{3-7} cycloalkyl (such as cyclopropyl), C_1 - C_6 alkoxycarbonyl (such as methoxycarbonyl) and phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl (such as CF_3), phenyl(C_1 - C_6

alkyl) (such as benzyl), C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, S(O)₂(C₁-C₆ alkyl), C(O)NH₂, carboxy or C₁-C₆ alkoxycarbonyl); or

R¹ represents C₂-C₆ alkenyl optionally substituted by phenyl (itself optionally substituted by one or more of halogen, nitro, cyano, C₁-C₆ alkyl, C₁-C₆ haloalkyl, phenyl(C₁-C₆ alkyl), C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, S(O)₂(C₁-C₆ alkyl), C(O)NH₂, carboxy or C₁-C₆ alkoxycarbonyl); or

R¹ represents a 3- to 14-membered saturated or unsaturated ring system which optionally comprises up to two ring carbon atoms that form carbonyl groups and which optionally further comprises up to 4 ring heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein the ring system is optionally substituted by one or more substituents independently selected from: halogen, cyano, nitro, oxo, hydroxyl, C₁-C₈ alkyl, C₁-C₆ hydroxyalkyl, C₁-C₆ haloalkyl, C₁-C₆ alkoxy(C₁-C₆ alkyl), C₃-C₇ cycloalkyl(C₁-C₆ alkyl), C₁-C₆ alkylthio(C₁-C₆ alkyl), C₁-C₆ alkylcarbonyloxy(C₁-C₆ alkyl), C₁-C₆ alkylS(O)₂(C₁-C₆ alkyl), aryl(C₁-C₆ alkyl), heterocyclyl(C₁-C₆ alkyl), arylS(O)₂(C₁-C₆ alkyl), heterocyclylS(O)₂(C₁-C₆ alkyl), aryl(C₁-C₆ alkyl)S(O)₂, heterocyclyl(C₁-C₆ alkyl)S(O)₂, C₂-C₆ alkenyl, C₁-C₆ alkoxy, carboxy-substituted C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, C₁-C₆ hydroxyalkoxy, C₁-C₆ alkylcarboxy-substituted C₁-C₆ alkoxy, aryloxy, heterocyclioxy, C₁-C₆ alkylthio, C₃-C₇ cycloalkyl(C₁-C₆ alkylthio), C₃-C₆ alkynylthio, C₁-C₆ alkylcarbonylamino, C₁-C₆ haloalkylcarbonylamino, SO₃H, -NR⁷R⁸, -C(O)NR²³R²⁴, S(O)₂NR¹⁸R¹⁹, S(O)₂R²⁰, R²⁵C(O), carboxyl, C₁-C₆ alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, oxo, hydroxy, nitro, cyano, C₁-C₆ alkyl, C₁-C₆ haloalkyl, phenyl(C₁-C₆ alkyl), C₁-C₆ alkoxy, C₁-C₆ haloalkoxy, S(O)₂(C₁-C₆ alkyl), C(O)NH₂, carboxy or C₁-C₆ alkoxycarbonyl;

m is 0 or 1;

Q represents an oxygen or sulphur atom or a group NR⁹, C(O), C(O)NR⁹, NR⁹C(O) or CH=CH;

n is 0, 1, 2, 3, 4, 5 or 6 provided that when n is 0, then m is 0;

each R² and R³ independently represents a hydrogen atom or a C₁-C₄ alkyl group, or

(CR²R³)_n represents C₃-C₇ cycloalkyl optionally substituted by C₁-C₄ alkyl;

T represents a group NR¹⁰, C(O)NR¹⁰, NR¹¹C(O)NR¹⁰ or C(O)NR¹⁰NR¹¹;

X^1 , X^2 , X^3 and X^4 are, independently, CH_2 , CHR^{12} {wherein each R^{12} is, independently, C_1 - C_4 alkyl or C_3 - C_7 cycloalkyl(C_1 - C_4 alkyl)} or $C=O$; or, when they are CHR^{12} , the R^{12} groups of X^1 and X^3 or X^4 , or, X^2 and X^3 or X^4 join to form a two or three atom chain which is CH_2CH_2 , $CH_2CH_2CH_2$, CH_2OCH_2 or CH_2SCH_2 ; provided always that at least two of X^1 , X^2 , X^3 and X^4 are CH_2 ;

R^4 and R^5 each independently represent a hydrogen atom or a C_1 - C_4 alkyl group;

R^6 is aryl or heterocyclyl, both optionally substituted by one or more of: halogen, cyano, nitro, oxo, hydroxyl, C_1 - C_8 alkyl, C_1 - C_6 hydroxyalkyl, C_1 - C_6 haloalkyl, C_1 - C_6 alkoxy(C_1 - C_6 alkyl), C_3 - C_7 cycloalkyl(C_1 - C_6 alkyl), C_1 - C_6 alkylthio(C_1 - C_6 alkyl), C_1 - C_6 alkylcarbonyloxy(C_1 - C_6 alkyl), C_1 - C_6 alkyl $S(O)_2$ (C_1 - C_6 alkyl), aryl(C_1 - C_6 alkyl), heterocyclyl(C_1 - C_6 alkyl), aryl $S(O)_2$ (C_1 - C_6 alkyl), heterocyclyl $S(O)_2$ (C_1 - C_6 alkyl), aryl(C_1 - C_6 alkyl) $S(O)_2$, heterocyclyl(C_1 - C_6 alkyl) $S(O)_2$, C_2 - C_6 alkenyl, C_1 - C_6 alkoxy, carboxy-substituted C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkoxy, C_1 - C_6 alkylcarboxy-substituted C_1 - C_6 alkoxy, aryloxy, heterocyclioxy, C_1 - C_6 alkylthio, C_3 - C_7 cycloalkyl(C_1 - C_6 alkylthio), C_3 - C_6 alkynylthio, C_1 - C_6 alkylcarbonylamino, C_1 - C_6 haloalkylcarbonylamino, SO_3H , $-NR^{16}R^{17}$, $-C(O)NR^{21}R^{22}$, $S(O)_2NR^{13}R^{14}$, $S(O)_2R^{15}$, $R^{26}C(O)$, carboxyl, C_1 - C_6 alkoxycarbonyl, aryl and heterocyclyl; wherein the foregoing aryl and heterocyclyl moieties are optionally substituted by one or more of halogen, nitro, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, phenyl(C_1 - C_6 alkyl), C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, $S(O)_2$ (C_1 - C_6 alkyl), $C(O)NH_2$, carboxy or C_1 - C_6 alkoxycarbonyl;

R^7 , R^8 , R^9 , R^{10} , R^{11} , R^{13} , R^{14} , R^{16} , R^{17} , R^{18} , R^{19} , R^{21} , R^{22} , R^{23} and R^{24} are, independently hydrogen, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, C_1 - C_6 hydroxyalkyl, C_3 - C_7 cycloalkyl, C_3 - C_7 cycloalkyl(C_1 - C_4 alkyl) or phenyl(C_1 - C_6 alkyl); and,

R^{15} and R^{20} are, independently, C_1 - C_6 alkyl, C_1 - C_6 hydroxyalkyl, C_3 - C_6 cycloalkyl, C_3 - C_7 cycloalkyl(C_1 - C_4 alkyl) or C_1 - C_6 alkyl optionally substituted by phenyl;

R^{25} and R^{26} are, independently, C_1 - C_6 alkyl or phenyl (optionally substituted by one or more of halogen, nitro, cyano, C_1 - C_6 alkyl, C_1 - C_6 haloalkyl, phenyl(C_1 - C_6 alkyl), C_1 - C_6 alkoxy, C_1 - C_6 haloalkoxy, $S(O)_2$ (C_1 - C_6 alkyl), $C(O)NH_2$, carboxy or C_1 - C_6 alkoxycarbonyl);

or a pharmaceutically acceptable salt thereof, or solvate thereof, or a solvate of a salt thereof;

provided that when T is C(O)NR¹⁰ and R¹ is optionally substituted phenyl then n is not 0, have activity as modulators of chemokine receptor activity.

There is an unmet need for MCHr1 antagonists that are more potent, more selective, more
5 bioavailable and produce less side effects than known compounds in this field.

Summary of the invention

It is an object of the present invention to provide compounds, which are useful in treating obesity and related disorders, psychiatric disorders, neurological disorders and pain. This
10 object has been reached in that a compound of formula I has been provided for use as a MCHr1 antagonist.

According to another aspect of the invention a pharmaceutical formulation is provided comprising a compound of formula I, and a pharmaceutically acceptable adjuvant, diluent
15 or carrier.

According to a further aspect of the invention, the use of a compound of formula I is provided, in the preparation of a medicament for the treatment or prophylaxis of conditions associated with obesity.

20 According to yet another aspect of the invention, a method is provided of treating obesity, psychiatric disorders, anxiety, anxio-depressive disorders, depression, bipolar disorder, ADHD, cognitive disorders, memory disorders, schizophrenia, epilepsy, and related conditions, and neurological disorders and pain related disorders, comprising administering
25 a pharmacologically effective amount of a compound of Formula I to a patient in need thereof.

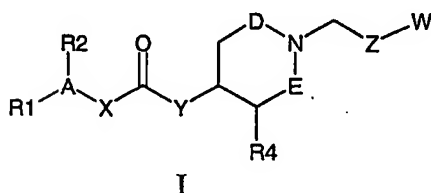
According to another aspect of the invention, a process for the preparation of compounds of formula I is provided.

30 According to a further aspect of the invention, a method is provided of treating obesity, type II diabetes, Metabolic syndrome and prevention of type II diabetes comprising

administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof.

Description of the invention

5 The invention relates to compounds of the general formula (I)



A represents N, a C₁₋₄ alkyl group, a C₂₋₄ alkenyl group, C₃₋₈ cycloalkyl, adamantyl, azetidiny, pyrrolidiny, piperidiny, piperaziny, morpholiny, 1,3 oxazidiny, tetrahydro-
 10 pyridiny, or spiro[indene-1,4'-piperidiny];

wherein said C₁₋₄ alkyl group or C₂₋₄ alkenyl group is optionally substituted by one or more fluoro;

X represents a bond or NR³,

wherein A and X do not both represent nitrogen;

15 wherein when A is azetidiny, 1,3 oxazidiny, pyrrolidiny, piperidiny, piperaziny, morpholiny, tetrahydropyridiny, or spiro[indene-1,4'-piperidiny]; the nitrogen atom in A is directly attached to C(O),

R¹ and R² independently represent H, C₁₋₆ alkyl, a C₂₋₆ alkenyl group, C₃₋₁₀ cycloalkyl, CONR^aR^b in which R^a and R^b independently represent H, a C₁₋₄ alkyl group or R^a and R^b,
 20 together with the nitrogen to which they are attached, form a 4 to 8 membered heterocyclic ring;

phenyl or naphthyl; or

a heterocyclic group selected from pyrrolyl, imidazolyl, furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl,
 25 pyridazinyl, quinolinyl, isoquinolinyl, quinazolyl, indolyl, benzofuranyl, benzo[b]thienyl, benzimidazolyl, benzothiazolyl, 1,4-benzodioxinyl, 1,3-benzodioxolyl, piperidiny, morpholiny, 1,4-oxazepanyl, or 4,4-dioxothiomorpholiny;

wherein R¹ or R² are optionally substituted by one or more of the following:

cyano

halo

hydroxy

oxo

a C₁₋₄ alkyl group optionally substituted by one or more fluoro;

5 a C₁₋₄ alkoxy group optionally substituted by one or more fluoro;

a group NCOR^aR^b or CONR^aR^b in which R^a and R^b independently represent a C₁₋₃ alkyl group;

a group SO₂C₁₋₄alkyl, optionally substituted by one or more fluoro;

an aryl or heteroaryl group selected from thiadiazolyl, pyrazolyl, phenyl, phenoxy, 2-
10 pyridyl or 3-pyridyl wherein said aryl or heteroaryl group may optionally be further substituted by one or more of the following:

cyano,

halo,

hydroxy,

15 a C₁₋₄ alkyl group optionally substituted by one or more fluoro;

a C₁₋₄ alkoxy group optionally substituted by one or more fluoro;

a group NCOR^aR^b or CONR^aR^b in which R^a and R^b independently represent a C₁₋₃ alkyl group;

a group SO₂C₁₋₄alkyl, optionally substituted by one or more fluoro;

20 R¹ and/or R² is optionally linked to A via oxygen or via a C₁₋₄ alkyl group, wherein one of the carbon atoms in said C₁₋₄ alkyl group optionally is replaced with an oxygen atom, Y represents NR³, C(R⁵, R⁶) or a bond,

wherein at least one of A, X or Y is N, NR³ or a nitrogen-containing heterocyclic ring, R³, R⁵ and R⁶ independently represent H or a C₁₋₄ alkyl group,

25 D represents (CH₂)_n, wherein n is 0 or 1 and E represents (CH₂)_m, wherein m is 0 or 1,

R⁴ represents H or, when m and n are both 1, R₄ represents H or F,

Z represents 2,5-thienyl, 2,5-furyl, or pyrrolyl, optionally substituted by one or more of the following: cyano, halo, a C₁₋₄ alkyl group optionally substituted by one or more fluoro, a C₁₋₄ alkoxy group optionally substituted by one or more fluoro,

30 W represents phenyl, 2-pyridyl or 3-pyridyl each of which is optionally substituted by one or more of the following: cyano, halo, a C₁₋₄ alkyl group optionally substituted by one or more fluoro, a C₁₋₄ alkoxy group optionally substituted by one or more fluoro, a

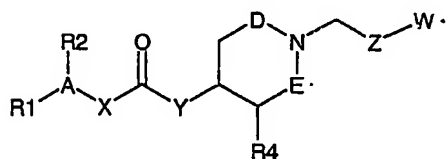
trifluoromethylsulfonyl or a 2, 2'-difluoro-oxolanyl group (fused with two adjacent aromatic carbon atoms in W),

as well as tautomers, optical isomers and racemates thereof as well as pharmaceutically acceptable salts thereof,

- 5 with the proviso that when Y represents NR^3 then A-X does not represent OCH_2 , CH_2CH_2 or $\text{CH}=\text{CH}$, wherein each of the carbon atom may optionally be substituted by 1 to 2 methyl groups and/or 1 to 2 fluoro.

The invention further relates to compounds of the general formula (Ia)

10



Ia

A represents N, a C_{1-4} alkyl group, a C_{2-4} alkenyl group, C_{3-8} cycloalkyl, adamantyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyridinyl, or spiro[indene-1,4'-piperidinyl];

- 15 wherein said C_{1-4} alkyl group or C_{2-4} alkenyl group is optionally substituted by one or more fluoro;

X represents a bond or NR^3 ,

wherein A and X do not both represent nitrogen;

wherein when A is pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyridinyl,

- 20 or spiro[indene-1,4'-piperidinyl]; the nitrogen atom in A is directly attached to $\text{C}(\text{O})$,

R^1 and R^2 independently represent H, C_{1-6} alkyl, a C_{2-6} alkenyl group, C_{3-8} cycloalkyl, CONR^aR^b in which R^a and R^b independently represent H, a C_{1-4} alkyl group or R^a and R^b , together with the nitrogen to which they are attached, form a 4 to 8 membered heterocyclic

- 25 ring;

phenyl or naphthyl; or

a heterocyclic group selected from pyrrolyl, imidazolyl, furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl,

pyridazinyl, quinolinyl, isoquinolyl, quinazolyl, indolyl, benzofuranyl, benzo[b]thienyl, benzimidazolyl, benzothiazolyl, 1,4-benzodioxinyl or 1,3-benzodioxolyl;

wherein R¹ or R² are optionally substituted by one or more of the following:

- cyano
- 5 halo
- hydroxy
- a C₁₋₄ alkyl group optionally substituted by one or more fluoro;
- a C₁₋₄ alkoxy group optionally substituted by one or more fluoro;
- a group NCOR^aR^b or CONR^aR^b in which R^a and R^b independently represent a C₁₋₃
- 10 alkyl group;
- a group SO₂C₁₋₄alkyl, optionally substituted by one or more fluoro;
- an aryl or heteroaryl group selected from thiadiazolyl, pyrazolyl, phenyl, phenoxy, 2-pyridyl or 3-pyridyl wherein said aryl or heteroaryl group may optionally be further substituted by one or more of the following:

- 15 cyano,
- halo,
- hydroxy,
- a C₁₋₄ alkyl group optionally substituted by one or more fluoro;
- a C₁₋₄ alkoxy group optionally substituted by one or more fluoro;
- 20 a group NCOR^aR^b or CONR^aR^b in which R^a and R^b independently represent a C₁₋₃ alkyl group;
- a group SO₂C₁₋₄alkyl, optionally substituted by one or more fluoro;

R¹ and/or R² is optionally linked to A via oxygen or via a C₁₋₄ alkyl group, wherein one of the carbon atoms in said C₁₋₄ alkyl group optionally is replaced with an oxygen atom,

- 25 Y represents NR³, C(R⁵, R⁶) or a bond,

wherein at least one of A, X or Y is N, NR³ or a nitrogen-containing heterocyclic ring,

R³, R⁵ and R⁶ independently represent H or a C₁₋₄ alkyl group,

D represents (CH₂)_n, wherein n is 0 or 1 and E represents (CH₂)_m, wherein m is 0 or 1,

R⁴ represents H or, when m and n are both 1, R₄ represents H or F,

- 30 Z represents 2,5-thienyl, 2,5-furyl, or pyrrolyl, optionally substituted by one or more of the following: cyano, halo, a C₁₋₄ alkyl group optionally substituted by one or more fluoro, a C₁₋₄ alkoxy group optionally substituted by one or more fluoro,

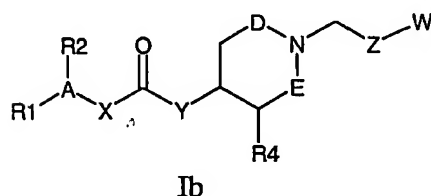
W represents phenyl, 2-pyridyl or 3-pyridyl each of which is optionally substituted by one or more of the following: cyano, halo, a C₁₋₄ alkyl group optionally substituted by one or more fluoro, a C₁₋₄ alkoxy group optionally substituted by one or more fluoro, a trifluoromethylsulfonyl or a 2, 2'-difluoro-oxolanyl group (fused with two adjacent aromatic carbon atoms in W),

as well as tautomers, optical isomers and racemates thereof as well as pharmaceutically acceptable salts thereof,

with the proviso that when Y represents NR³ then A-X does not represent OCH₂, CH₂CH₂ or CH=CH, wherein each of the carbon atom may optionally be substituted by 1 to 2 methyl groups and/or 1 to 2 fluoro.

In group A, R¹ and R² is either attached to the same atom or to different atoms.

The invention further relates to compounds of formula Ib



A represents azetidiny, or 1,3 oxazidiny,

X represents a bond,

wherein the nitrogen atom in A is directly attached to C(O),

R¹ and R² independently represent H, C₁₋₆ alkyl, a C₂₋₆ alkenyl group, C₃₋₁₀ cycloalkyl, CONR^aR^b in which R^a and R^b independently represent H, a C₁₋₄ alkyl group or R^a and R^b, together with the nitrogen to which they are attached, form a 4 to 8 membered heterocyclic ring;

phenyl or naphthyl; or

a heterocyclic group selected from pyrrolyl, imidazolyl, furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinolinyl, isoquinolyl, quinazolyl, indolyl, benzofuranyl, benzo[b]thienyl, benzimidazolyl, benzothiazolyl, 1,4-benzodioxinyl, 1,3-benzodioxolyl, piperidinyl, morpholinyl, 1,4-oxazepanyl, or 4,4-dioxothiomorpholinyl;

wherein R^1 or R^2 are optionally substituted by one or more of the following:

cyano

halo

hydroxy

5 a C_{1-4} alkyl group optionally substituted by one or more fluoro;

a C_{1-4} alkoxy group optionally substituted by one or more fluoro;

a group $NCOR^aR^b$ or $CONR^aR^b$ in which R^a and R^b independently represent a C_{1-3} alkyl group;

a group $SO_2C_{1-4}alkyl$, optionally substituted by one or more fluoro;

10 an aryl or heteroaryl group selected from thiadiazolyl, pyrazolyl, phenyl, phenoxy, 2-pyridyl or 3-pyridyl wherein said aryl or heteroaryl group may optionally be further substituted by one or more of the following:

cyano,

halo,

15 hydroxy,

a C_{1-4} alkyl group optionally substituted by one or more fluoro;

a C_{1-4} alkoxy group optionally substituted by one or more fluoro;

a group $NCOR^aR^b$ or $CONR^aR^b$ in which R^a and R^b independently represent a C_{1-3} alkyl group;

20 a group $SO_2C_{1-4}alkyl$, optionally substituted by one or more fluoro;

R^1 and/or R^2 is optionally linked to A via oxygen or via a C_{1-4} alkyl group, wherein one of the carbon atoms in said C_{1-4} alkyl group optionally is replaced with an oxygen atom,

Y represents NR^3 , $C(R^5, R^6)$ or a bond,

wherein at least one of A, X or Y is N, NR^3 or a nitrogen-containing heterocyclic ring,

25 R^3 , R^5 and R^6 independently represent H or a C_{1-4} alkyl group,

D represents $(CH_2)_n$, wherein n is 0 or 1 and E represents $(CH_2)_m$, wherein m is 0 or 1,

R^4 represents H or, when m and n are both 1, R_4 represents H or F,

Z represents 2,5-thienyl, 2,5-furyl, or pyrrolyl, optionally substituted by one or more of the following: cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, a

30 C_{1-4} alkoxy group optionally substituted by one or more fluoro,

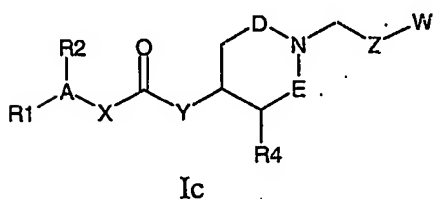
W represents phenyl, 2-pyridyl or 3-pyridyl each of which is optionally substituted by one or more of the following: cyano, halo, a C_{1-4} alkyl group optionally substituted by one or

more fluoro, a C₁₋₄ alkoxy group optionally substituted by one or more fluoro, a trifluoromethylsulfonyl or a 2, 2'-difluoro-oxolanyl group (fused with two adjacent aromatic carbon atoms in W),

as well as tautomers, optical isomers and racemates thereof as well as pharmaceutically acceptable salts thereof,

with the proviso that when Y represents NR³ then A-X does not represent OCH₂, CH₂CH₂ or CH=CH, wherein each of the carbon atom may optionally be substituted by 1 to 2 methyl groups and/or 1 to 2 fluoro.

The invention further relates to compounds of formula Ic



A represents N, a C₁₋₄ alkyl group, a C₂₋₄ alkenyl group, C₃₋₈ cycloalkyl, adamantyl, azetidiny, pyrrolidiny, piperidiny, piperaziny, morpholiny, 1,3 oxazidiny, tetrahydro-
pyridiny, or spiro[indene-1,4'-piperidiny];

wherein said C₁₋₄ alkyl group or C₂₋₄ alkenyl group is optionally substituted by one or more fluoro;

X represents a bond or NR³,

wherein A and X do not both represent nitrogen;

wherein when A is azetidiny, 1,3 oxazidiny, pyrrolidiny, piperidiny, piperaziny, morpholiny, tetrahydropyridiny, or spiro[indene-1,4'-piperidiny]; the nitrogen atom in A is directly attached to C(O),

R¹ and R² independently represent C₉₋₁₀ cycloalkyl; or

a heterocyclic group selected from piperidiny, morpholiny, 1,4-oxazepany, or 4,4-dioxothiomorpholiny;

wherein R¹ or R² are optionally substituted by one or more of the following:

cyano

halo

hydroxy

a C₁₋₄ alkyl group optionally substituted by one or more fluoro;
a C₁₋₄ alkoxy group optionally substituted by one or more fluoro;
a group NCOR^aR^b or CONR^aR^b in which R^a and R^b independently represent a C₁₋₃ alkyl group;
5 a group SO₂C₁₋₄alkyl, optionally substituted by one or more fluoro;
an aryl or heteroaryl group selected from thiadiazolyl, pyrazolyl, phenyl, phenoxy, 2-pyridyl or 3-pyridyl wherein said aryl or heteroaryl group may optionally be further substituted by one or more of the following:

cyano,

10 halo,

hydroxy,

a C₁₋₄ alkyl group optionally substituted by one or more fluoro;

a C₁₋₄ alkoxy group optionally substituted by one or more fluoro;

a group NCOR^aR^b or CONR^aR^b in which R^a and R^b independently represent a
15 C₁₋₃ alkyl group;

a group SO₂C₁₋₄alkyl, optionally substituted by one or more fluoro;

R¹ and/or R² is optionally linked to A via oxygen or via a C₁₋₄ alkyl group, wherein one of the carbon atoms in said C₁₋₄ alkyl group optionally is replaced with an oxygen atom,

Y represents NR³, C(R⁵·R⁶) or a bond,

20 wherein at least one of A, X or Y is N, NR³ or a nitrogen-containing heterocyclic ring,
R³, R⁵ and R⁶ independently represent H or a C₁₋₄ alkyl group,

D represents (CH₂)_n, wherein n is 0 or 1 and E represents (CH₂)_m, wherein m is 0 or 1,

R⁴ represents H or, when m and n are both 1, R₄ represents H or F,

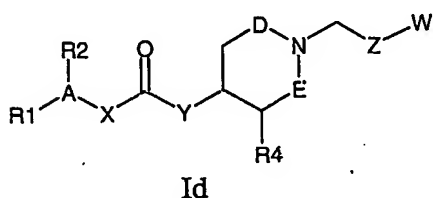
Z represents 2,5-thienyl, 2,5-furyl, or pyrrolyl, optionally substituted by one or more of the
25 following: cyano, halo, a C₁₋₄ alkyl group optionally substituted by one or more fluoro, a C₁₋₄ alkoxy group optionally substituted by one or more fluoro,

W represents phenyl, 2-pyridyl or 3-pyridyl each of which is optionally substituted by one or more of the following: cyano, halo, a C₁₋₄ alkyl group optionally substituted by one or more fluoro, a C₁₋₄ alkoxy group optionally substituted by one or more fluoro, a
30 trifluoromethylsulfonyl or a 2, 2'-difluoro-oxolanyl group (fused with two adjacent aromatic carbon atoms in W),

as well as tautomers, optical isomers and racemates thereof as well as pharmaceutically acceptable salts thereof,

with the proviso that when Y represents NR^3 then A-X does not represent OCH_2 , CH_2CH_2 or $\text{CH}=\text{CH}$, wherein each of the carbon atom may optionally be substituted by 1 to 2 methyl groups and/or 1 to 2 fluoro.

The invention further relates to compounds of the general formula (Id)



- 10 A represents N, a C_{1-4} alkyl group, a C_{2-4} alkenyl group, C_{3-8} cycloalkyl, adamantyl, azetidiny, pyrrolidiny, piperidiny, piperaziny, morpholiny, 1,3 oxazidiny, tetrahydropyridiny, or spiro[indene-1,4'-piperidiny];
wherein said C_{1-4} alkyl group or C_{2-4} alkenyl group is optionally substituted by one or more fluoro;

- 15 X represents a bond or NR^3 ,
wherein A and X do not both represent nitrogen;
wherein when A is azetidiny, 1,3 oxazidiny, pyrrolidiny, piperidiny, piperaziny, morpholiny, tetrahydropyridiny, or spiro[indene-1,4'-piperidiny]; the nitrogen atom in A is directly attached to $\text{C}(\text{O})$,

- 20 R^1 and R^2 independently represent H, C_{1-6} alkyl, a C_{2-6} alkenyl group, C_{3-10} cycloalkyl, CONR^aR^b in which R^a and R^b independently represent H, a C_{1-4} alkyl group or R^a and R^b , together with the nitrogen to which they are attached, form a 4 to 8 membered heterocyclic ring;

phenyl or naphthyl; or

- 25 a heterocyclic group selected from pyrrolyl, imidazolyl, furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinoliny, isoquinolyl, quinazolyl, indolyl, benzofuranyl, benzo[b]thienyl, benzimidazolyl, benzothiazolyl, 1,4-benzodioxinyl, 1,3-benzodioxolyl, piperidiny, morpholiny, 1,4-oxazepanyl, or 4,4-dioxothiomorpholiny;

wherein R^1 and/or R^2 are substituted by oxo,

R^1 and/or R^2 is optionally linked to A via oxygen or via a C_{1-4} alkyl group, wherein one of the carbon atoms in said C_{1-4} alkyl group optionally is replaced with an oxygen atom,

Y represents NR^3 , $C(R^5 \cdot R^6)$ or a bond,

5 wherein at least one of A, X or Y is N, NR^3 or a nitrogen-containing heterocyclic ring,

R^3 , R^5 and R^6 independently represent H or a C_{1-4} alkyl group,

D represents $(CH_2)_n$, wherein n is 0 or 1 and E represents $(CH_2)_m$, wherein m is 0 or 1,

R^4 represents H or, when m and n are both 1, R_4 represents H or F,

Z represents 2,5-thienyl, 2,5-furyl, or pyrrolyl, optionally substituted by one or more of the
10 following: cyano, halo, a C_{1-4} alkyl group optionally substituted by one or more fluoro, a
 C_{1-4} alkoxy group optionally substituted by one or more fluoro,

W represents phenyl, 2-pyridyl or 3-pyridyl each of which is optionally substituted by one
or more of the following: cyano, halo, a C_{1-4} alkyl group optionally substituted by one or
more fluoro, a C_{1-4} alkoxy group optionally substituted by one or more fluoro, a
15 trifluoromethylsulfonyl or a 2, 2'-difluoro-oxolanyl group (fused with two adjacent
aromatic carbon atoms in W),

as well as tautomers, optical isomers and racemates thereof as well as pharmaceutically
acceptable salts thereof,

with the proviso that when Y represents NR^3 then A-X does not represent OCH_2 , CH_2CH_2
20 or $CH=CH$, wherein each of the carbon atom may optionally be substituted by 1 to 2
methyl groups and/or 1 to 2 fluoro.

Particular groups now follow in which some of X, Y, Z, W, and R^1 in compounds of
formula I-Ib are further defined. It will be understood that such group definitions may be
25 used where appropriate with any of the other group definitions, claims or embodiments
defined hereinbefore or hereinafter.

In another group of compounds of formula I-Ib, all compounds covered by claim 1 in WO
01/14333 are excluded.

30

In a particular group of compounds of formula I, Z represents 1,3-1H pyrrolyl (in which
the heteroatom is connected to W).

In another particular group of compounds of formula I, W is phenyl or 2- or 3-pyridyl substituted by trifluoromethyl. In one further group of compounds of formula I, W is phenyl or 2-substituted by trifluoromethyl.

5

In a further group of compounds of formula I, Y is CH₂.

In another group of compounds of formula I, Y is a bond.

10

In another group of compounds of formula I, Y is NH.

In yet another group of compounds of formula I, A is NH, X is a bond and Y is CH₂.

15

In a further particular group of compounds of formula I, A is C₁₋₄ alkyl, X is NH and Y is CH₂.

In another particular group of compounds of formula I, A is NH, X is a bond and Y is a bond.

20

In a further group of compounds of formula I, X is NH and Y is a bond.

In a further particular group of compounds of formula I, A is C₁₋₄ alkyl, X is NH and Y is a bond.

25

In another particular group of compounds of formula I, D represents (CH₂)_n, wherein n is 1 and E represents (CH₂)_m, wherein m is 1.

In another particular group of compounds of formula I, D represents (CH₂)_n, wherein n is 1 and E represents (CH₂)_m, wherein m is 0, or vice versa.

30

In another particular group of compounds of formula I, D represents (CH₂)_n, wherein n is 0 and E represents (CH₂)_m, wherein m is 0.

In another particular group of compounds of formula I, A represents pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl.

5 In another particular group of compounds of formula I, A represents piperidinyl.

The term "pharmaceutically acceptable salt" refers to pharmaceutically acceptable acid addition salts. A suitable pharmaceutically acceptable salt of a compound of Formula I is, for example, an acid-addition salt of a compound of Formula I which is sufficiently basic,
10 for example an acid-addition salt with an inorganic or organic acid such as:

(1S)-(+)-10-camphorsulfonic acid; cyclohexylsulfonic acid; phosphoric acid; dimethylphosphoric acid; p-toluenesulfonic acid; L-lysine; L-lysine hydrochloride; saccharinic acid; methanesulfonic acid; hydrobromic acid; hydrochloric acid; sulphuric acid; 1,2-ethanedisulfonic acid; (+/-)-camphorsulfonic acid; ethanesulfonic acid; nitric
15 acid; p-xylenesulfonic acid; 2-mesitylenesulfonic acid; 1,5-naphthalenedisulfonic acid; 1-naphthalenesulfonic acid; 2-naphthalenesulfonic acid; benzenesulfonic acid; maleic acid; D-glutamic acid; L-glutamic acid; D,L-glutamic acid; L-arginine; glycine; salicylic acid; tartaric acid; fumaric acid; citric acid; L-(-)-malic acid; D,L-malic acid and D-gluconic acid.

20 Throughout the specification and the appended claims, a given chemical formula or name shall encompass all tautomers, all stereo and optical isomers and racemates thereof as well as mixtures in different proportions of the separate enantiomers, where such isomers and enantiomers exist, as well as pharmaceutically acceptable salts thereof. Isomers may be
25 separated using conventional techniques, e.g. chromatography or fractional crystallisation. The enantiomers may be isolated by separation of racemate for example by fractional crystallisation, resolution or HPLC. The diastereomers may be isolated by separation of isomer mixtures for instance by fractional crystallisation, HPLC or flash chromatography. Alternatively the stereoisomers may be made by chiral synthesis from chiral starting
30 materials under conditions, which will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent. All stereoisomers are included within the scope of the invention.

Compounds of the present invention are intended to be chemically stable and it is assumed that it is within the skilled persons knowledge to identify which combinations of the above-defined groups in Formula I that may result in chemically unstable compounds of Formula
5 1.

The following definitions shall apply throughout the specification and the appended claims.

10 Unless otherwise stated or indicated, the term "alkyl" denotes either a straight chain or branched alkyl group. Examples of said alkyl include methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, iso-butyl, sec-butyl and t-butyl. Preferred alkyl groups are methyl, ethyl, propyl, isopropyl and tertiary butyl.

15 Unless otherwise stated or indicated, the term "alkenyl" denotes either a straight chain or branched alkenyl group wherein said group contains one or more double bonds.

Unless otherwise stated or indicated, the term "alkoxy" denotes a group O-alkyl, wherein alkyl is as defined above.

20 Unless otherwise stated or indicated, the term "halo" shall mean fluorine, chlorine, bromine or iodine.

Specific compounds of the invention include one or more of the following:

25 2,2-diphenyl-*N*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,

N-(3,4-difluorobenzyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,

N-(2-phenylethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidine-4-
30 carboxamide,

- N*-[bis(4-fluorophenyl)methyl]-2-[1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide,
- N,N*-bis(4-fluorophenyl)-*N'*-[1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea,
- 5 *N*-[bis(4-fluorophenyl)methyl]-2-[1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl)methyl}pyrrolidin-3-yl]acetamide,
- N*-(4-fluorophenyl)-1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide acetate,
- N*-(1,3-benzothiazol-2-ylmethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide,
- 10 *N*-(2-furylmethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide,
- N*-(2-pyridin-2-ylethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide,
- 15 *N*-(2,4-dichlorobenzyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide,
- N*-(1,2-diphenylethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide
- N*-(1,3-benzodioxol-5-ylmethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide,
- 20 *N*-ethyl-*N*-(2-pyridin-2-ylethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide,
- N*-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide,
- 25 *N*-[3-(1*H*-imidazol-1-yl)propyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide,
- N*-(2,4-dichlorobenzyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide,
- N*-(4-fluorophenyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide,
- 30

- N-[phenyl(pyridin-2-yl)methyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- N-[3-(difluoromethoxy)benzyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- 5 1-(3-methoxyphenyl)-4-{{1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl}acetyl}piperazine,
- 1'-{{1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl}acetyl}spiro[indene-1,4'-piperidine],
- N-(3,3-diphenylpropyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- 10 N-(1-phenylpropyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide
- N-(4-fluorophenyl)-N-methyl-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide
- 15 N-[(1*R*,2*S*)-2-phenylcyclopropyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- N-(3-methylbutyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methyl-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide
- 20 N-[2-(3,4-dimethoxyphenyl)ethyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- N-[4-(1,2,3-thiadiazol-4-yl)benzyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- 25 N-[1-(2,3-dihydro-1,4-benzodioxin-5-yl)ethyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- N,N-diethyl-1-{{1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl}acetyl}piperidine-3-carboxamide,
- N-1-adamantyl-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- 30

- N-[2-(4-methoxyphenoxy)ethyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide
- N-((1*S*)-1-[(benzyloxy)methyl]propyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide
- 5 N-[(1*R*)-1-(3-methoxyphenyl)ethyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide
- N-({[3-(4-methoxyphenyl)isoxazol-5-yl]methyl}-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide
- 4-(4-chlorophenyl)-1-({1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetyl)-1,2,3,6-tetrahydropyridine
- 10 N-[(1*S*,2*S*)-2-(benzyloxy)cyclopentyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide
- N-(1-methyl-1-phenylethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide
- 15 N-[(1-methyl-1*H*-pyrrol-2-yl)methyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide
- 4-(2-oxo-2-pyrrolidin-1-ylethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidine,
- N-(2-pyridin-2-ylethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidine-4-carboxamide,
- 20 N-(2,4-dichlorobenzyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidine-4-carboxamide,
- N-(1,2-diphenylethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidine-4-carboxamide,
- 25 N-(1,3-benzodioxol-5-ylmethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidine-4-carboxamide,
- N-[2-(3,4-dimethoxyphenyl)ethyl]-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidine-4-carboxamide,

- N-[4-(1,2,3-thiadiazol-4-yl)benzyl]-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidine-4-carboxamide,
- N-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidine-4-carboxamide,
- 5 N-[1-(2,3-dihydro-1,4-benzodioxin-5-yl)ethyl]-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidine-4-carboxamide,
- N-[phenyl(pyridin-2-yl)methyl]-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidine-4-carboxamide,
- N-[3-(difluoromethoxy)benzyl]-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidine-4-carboxamide,
- 10 N-[2-(4-methoxyphenoxy)ethyl]-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidine-4-carboxamide,
- N-[(1*S*)-1-[(benzyloxy)methyl]propyl]-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidine-4-carboxamide,
- 15 N-[[3-(4-methoxyphenyl)isoxazol-5-yl]methyl]-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidine-4-carboxamide,
- 1-(3-methoxyphenyl)-4-{[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]carbonyl}piperazine,
- 4-(4-chlorophenyl)-1-{[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]carbonyl}-1,2,3,6-tetrahydropyridine,
- 20 N-[(1*S*,2*S*)-2-(benzyloxy)cyclopentyl]-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidine-4-carboxamide,
- N-(3,3-diphenylpropyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidine-4-carboxamide,
- 25 N-(1-phenylpropyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidine-4-carboxamide,
- N-(1,3-benzothiazol-2-ylmethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidine-4-carboxamide,

- N*-[(5-chloro-6-methoxypyridin-3-yl)(4-fluorophenyl)methyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide,
- N*-[(5-chloro-6-oxo-1,6-dihydropyridin-3-yl)(4-fluorophenyl)methyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide acetate salt,
- 5 *N*-(4-chloro-2-methoxybenzyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide,
- N*-(4-chloro-2-hydroxybenzyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide, acetate salt,
- 2-(3-fluorophenyl)-*N*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]pyrrolidine-1-carboxamide,
- 10 *N*-[2-(1*H*-imidazol-1-yl)-1-phenylethyl]-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea,
- N*-(3-fluorobenzyl)-*N*-methyl-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea,
- 15 3-(1,1-dioxidothiomorpholin-4-yl)-*N*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]azetidine-1-carboxamide,
- N*-(3-hydroxybutyl)-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea,
- N*-[(1*S*)-2-hydroxy-1-phenylethyl]-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea,
- 20 2-(1,3-benzothiazol-2-yl)-*N*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]pyrrolidine-1-carboxamide,
- 2-(pyridin-3-ylmethyl)-*N*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]pyrrolidine-1-carboxamide,
- 25 (+)-2-(3-fluorophenyl)-*N*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]pyrrolidine-1-carboxamide,
- (-)-2-(3-fluorophenyl)-*N*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]pyrrolidine-1-carboxamide,

- (+)-*N*-[2-(1*H*-imidazol-1-yl)-1-phenylethyl]-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea,
- (-)-*N*-[2-(1*H*-imidazol-1-yl)-1-phenylethyl]-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea,
- 5 2-(2-hydroxyethyl)-*N*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]piperidine-1-carboxamide;
- N*-(4-fluorobenzyl)-*N*-(3-hydroxypropyl)-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea;
- N*-(2-hydroxy-3-phenoxypropyl)-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea;
- 10 *N*-[(1-hydroxycyclohexyl)methyl]-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea;
- N*-[(4-fluorophenyl)(6-methoxypyridin-3-yl)methyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide;
- 15 *N*-[(4-fluorophenyl)(6-oxo-1,6-dihydropyridin-3-yl)methyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide; and
- N*-[2-(2-methyl-1*H*-imidazol-1-yl)-1-phenylethyl]-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea;
- and pharmaceutically acceptable salts thereof.

20

In one further aspect of the invention, there is provided *N*-[4-(trifluoromethoxy)phenyl]-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea.

In yet one further aspect of the invention, there is provided *N*-(2,4-dichlorophenyl)-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea, and pharmaceutically acceptable salts thereof.

25

In another aspect of the invention, there is provided *N*-1-naphthyl-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea, and pharmaceutically acceptable salts thereof.

- 5 In yet another aspect of the invention, there is provided *N*-(3-fluorobenzyl)-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea, and pharmaceutically acceptable salts thereof.

- 10 In one further aspect of the invention, there is provided *N*-(diphenylmethyl)-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea, and pharmaceutically acceptable salts thereof.

- In another aspect of the invention, there is provided *N*-methyl-*N*-phenyl-*N'*-[1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea and pharmaceutically acceptable salts thereof.
- 15

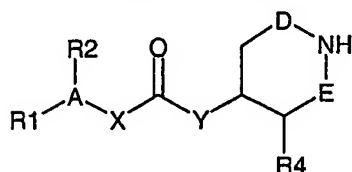
Another particular group of Formula I comprises compounds in which A is C₁ alkyl, X is NH and Y is NH.

20 Methods of preparation

The compounds of the invention may be prepared as outlined below according to any of the following methods. However, the invention is not limited to these methods, the compounds may also be prepared as described for structurally related compounds in the prior art.

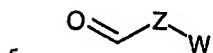
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Compounds of formula I may be prepared by reacting a compound of formula II



II

in which R^1 , R^2 , R^4 , A, X, Y, D, and E are as previously defined,
with a compound of formula III

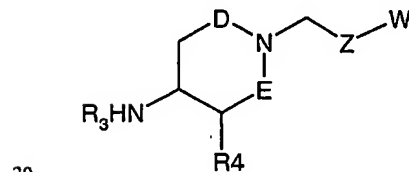


III

in which Z and W are as previously defined.

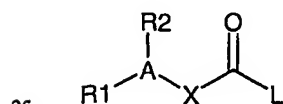
For example, a compound of formula II and a compound of formula III may be reacted
10 together at a temperature in the range of 0°C to 150°C, preferably in the range of 20°C to
80°C in the presence of a solvent, for example methanol, DCM, $CHCl_3$, THF or dioxane, in
the presence of a reducing agent, for example sodium cyanoborohydride (optionally
polymer supported) or sodium triacetoxyborohydride (optionally polymer supported).
Optionally, a catalytic amount of an acid, e.g. acetic acid, may be added to the reaction
15 mixture.

Alternatively, compounds of formula I, in which Y represents NR^3 , may be prepared by
reacting a compound of formula IV,



IV

in which R^3 , R^4 , D, E, Z and W are as previously defined, with a compound of formula V



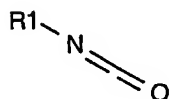
V

in which R^1 , R^2 , A and X are as previously defined, L represents a leaving group such as chloride or (provided that A-X does not represent N) a hydroxy group.

For example, a compound of formula IV and a compound of formula V, in which L is a hydroxy group, may be reacted together at a temperature in the range of 0°C to 150°C, preferably in the range of 20°C to 80°C in the presence of a solvent, for example THF, DCM, DCM/water (i.e. a two phase system) or DMF, optionally in the presence of a suitable inorganic or organic base, e.g. DIPEA or TEA, and a standard amide coupling reagent, e.g. HATU, TBTU, TFFH, PyBroP, EDC, or DCC, the latter two of which may optionally be polymer supported. Suitable additives such as HOBt and HOAt may also be optionally utilised.

Alternatively, compounds of formula I may be obtained by reaction of compounds of formula IV with compounds of formula V, in which L is chloride, in an inert solvent, e.g. THF, dioxane, DCM, $CHCl_3$ or 1,2-dichloroethane in the presence of a suitable inorganic or organic base, e.g. DIPEA, TEA, collidine, K_2CO_3 or $NaHCO_3$.

Alternatively, compounds of formula I in which $A=C$ and $X=N$, or in which $A=N$ and $X=bond$, Y represents NR^3 and in which R^2 is hydrogen, may be prepared by reacting a compound of formula IV, with a compound of formula VI



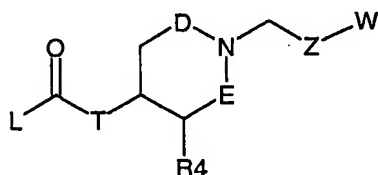
VI

in which R^1 is as previously defined (provided that R^1 is not H)

For example, a compound of formula IV and a compound of formula VI may be reacted together at a temperature in the range of 20°C to 80°C in the presence of a dry, inert solvent, for example THF or DCM, optionally in the presence of a suitable inorganic or organic base, e.g. DIPEA or TEA.

Alternatively, compounds of formula I, in which A represents a C₁₋₄ alkyl group (straight chain or branched) and X represents NR³, or in which A represents N and X represents a bond, and in which Y represents a bond or a C(R³)₂ group, may be prepared by reacting a compound of formula VII,

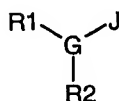
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VII

in which R⁴, D, E, Z and W are as previously defined, L is a hydroxy group or a leaving group such as chloride or fluoride and in which T represents a bond or a C(R³)₂-group with a compound of formula VIII,

10



VIII

in which G represents N and J represents H, or in which G represents a C₁₋₄ alkyl group (straight chain or branched) and J represents NR³, and in which R¹, R² and R³ are as previously defined,

15

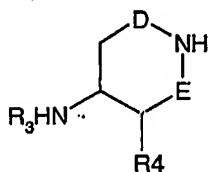
For example, a compound of formula VII and a compound of formula VIII, in which L is a hydroxy group, may be reacted together at a temperature in the range of 0°C to 150°C, preferably in the range of 20°C to 80°C in the presence of a solvent, for example THF, DCM, DCM/water (i.e. a two phase system) or DMF, optionally in the presence of a suitable inorganic or organic base, e.g. DIPEA or TEA, and a standard amide coupling reagent, e.g. HATU, TBTU, TFFH, PyBroP, EDC, or DCC, the latter two of which may optionally be polymer supported. Suitable additives such as HOBt and HOAt may also be optionally utilised.

20
25

Alternatively, compounds of formula I may be obtained by reaction of compounds of formula VII, in which L is chloride, with compounds of formula VIII in an inert solvent, e.g. THF, dioxane, DCM, CHCl_3 or 1,2-dichloroethane in the presence of a suitable inorganic or organic base, e.g. DIPEA, TEA, collidine, K_2CO_3 or NaHCO_3 .

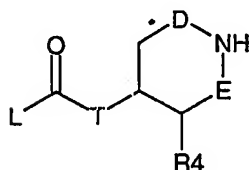
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Using methods similar to those described hereinbefore, compounds of formula II, in which B represents NR^3 , may be prepared by reaction of compounds of formula IX with compounds of formula V or VI



10 IX

Alternatively, using methods similar to those described hereinbefore, compounds of formula II, in which Y represents a bond or a $\text{C}(\text{R}^3)_2$ group, may be prepared by reacting a compound of formula X in which R^4 , D, E, L and T are as previously defined



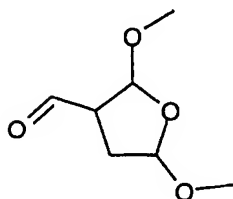
15

X

with a compound of formula VIII

Compounds of formula III, in which Z is a 1H-pyrrol-3-yl ring, may be prepared by reaction of a compound of formula XI with a compound of formula XII in which W is as previously defined.

20



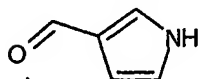
XI



XII

For example, a compound of formula XI and a compound of formula XII may be reacted together at a temperature in the range of 20°C to 90°C in acetic acid.

- 5 Alternatively, compounds of formula III, in which Z is a 1H-pyrrol-3-yl ring, may be prepared by reaction of a compound of formula XIII with a compound of formula XIV in which W is as previously defined and in which U is chloride or a bromide



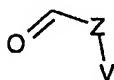
XIII



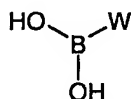
XIV

- 10 For example, a compound of formula XV and a compound of formula XVI may be reacted together in an inert solvent such as THF or dioxane in the presence of a strong base, e.g. NaH, at a temperature in the range of 20°C to 60°C.

Alternatively, compounds of formula III may be prepared by reaction of a compound of
15 formula XV, in which Z is as previously defined and in which V is bromide or iodide with a compound of formula XVI in which W is as previously defined.



XV

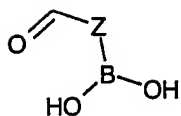


XVI

20

For example, a compound of formula XV and a compound of formula XVI may be reacted together under palladium catalysis using a method described e.g. in Feuerstein, M. et al., *Tetrahedron Lett.* 42 (33), 5659, 2001.

- 25 Alternatively, using similar synthetic methodology, compounds of formula III may be prepared by reaction of a compound of formula XVII, in which Z is as previously defined with a compound of formula XVIII in which W and V are as previously defined



XVII



XVIII

Using methods similar to those hereinbefore described, compounds of formulae IV and VII
 5 may be prepared by reaction of compounds of formulae IX and X respectively, with a compound of formula III.

Compounds of formula IX and X, in which R⁴ represents a fluorine atom (and D and E are both representing CH₂) may be prepared starting with fluorination (using e.g.
 10 SELECTFLUOR™ Reagent) of the silyl enol ether of piperidone, as described e.g. by van Neil, M.B. et al. *J. Med. Chem.* 1999, 42, 2087-2104. Reductive amination of the so formed α-fluoro piperidone gives compounds of formula IX. Preparation of compounds of formula X, where T represents CH₂, from α-fluoro piperidone may be carried out by standard methods, e.g. as described in PCT Int. Appl. WO2001000206. Additionally,
 15 compounds of formula X, where T represents a bond, could conceivably be prepared in analogy to chemistry described e.g. by Borne, R.F. et al. *J. Heterocyclic Chemistry* (1990), 27(2), 375-84.

Compounds of formula III, V, VI and VIII-XVIII are either commercially available or can
 20 be prepared by methods well known to those skilled in the art, e.g. as described hereinafter in the Experimental Section.

Optionally, the nitrogen of the ring in formulae IX and X may be protected prior to reaction with a compound of formula V and VIII. Amine protecting groups are known to those
 25 skilled in the art, for example the benzyl, t-Boc, or Cbz groups.

Optionally, the carboxylic acid in compounds of formula X may be protected as an ester prior to reaction with a compound of formula III. Suitable esters are e.g. ethyl, *tert*-butyl or benzyl esters.

The compounds of the invention may be isolated from their reaction mixtures using conventional techniques. Stereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. Enantiomers may be isolated by separation of racemate for example by fractional crystallisation, resolution or HPLC. The diastereomers may be isolated by separation of isomer mixtures for instance by fractional crystallisation, HPLC or flash chromatography. Alternatively the stereoisomers may be made by chiral synthesis from chiral starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, with a chiral reagent.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative and in some occasions, more convenient manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (*i.e.* chemical transformations may be performed upon different intermediates to those associated hereinbefore with a particular reaction).

Pharmaceutical preparations

The compounds of the invention will normally be administered via the oral, parenteral, intravenous, intramuscular, subcutaneous or in other injectable ways, buccal, rectal, vaginal, transdermal and/or nasal route and/or via inhalation, in the form of pharmaceutical preparations comprising the active ingredient either as a free base, or a pharmaceutically acceptable inorganic or organic addition salt, in a pharmaceutically acceptable dosage form. Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

Suitable daily doses of the compounds of the invention in the therapeutic treatment of humans are about 0.001-10 mg/kg body weight, preferably 0.01-3 mg/kg body weight.

Oral formulations are preferred particularly tablets or capsules which may be formulated by methods known to those skilled in the art to provide doses of the active compound in the range of 0.5 mg to 500mg for example 1 mg, 3 mg, 5 mg, 10 mg, 25 mg, 50 mg, 100 mg and 250 mg.

According to a further aspect of the invention there is also provided a pharmaceutical formulation including any of the compounds of the invention, or pharmaceutically acceptable derivatives thereof, in admixture with pharmaceutically acceptable adjuvants, diluents and/or carriers.

The compounds of the invention may also be combined with other therapeutic agents, which are useful in the treatment of disorders associated with obesity, psychiatric disorders, neurological disorders and pain.

Pharmacological properties

The compounds of formula (I) are useful for the treatment of obesity, psychiatric disorders such as psychotic disorders, anxiety, anxio-depressive disorders, depression, cognitive disorders, memory disorders, schizophrenia, epilepsy, and related conditions, and neurological disorders such as dementia, multiple sclerosis, Raynaud's syndrome, Parkinson's disease, Huntington's chorea and Alzheimer's disease. The compounds are also potentially useful for the treatment of immune, cardiovascular, reproductive and endocrine disorders, and diseases related to the respiratory and gastrointestinal systems. The compounds are also potentially useful as agents for ceasing consumption of tobacco, treating nicotine dependence and/or treating nicotine withdrawal symptoms, reducing the craving for nicotine and as anti-smoking agents. The compounds may also eliminate the increase in weight that normally accompanies the cessation of smoking. The compounds are also potentially useful as agents for treating or preventing diarrhea.

The compounds are also potentially useful as agents for reducing the craving/relapse for addictive substances that include, but are not limited to psychomotor-active agents such as nicotine, alcohol, cocaine, amphetamines, opiates, benzodiazepines and barbiturates. The compounds are also potentially useful as agents for treating drug addiction and/or drug abuse.

Accordingly, it is desirable to provide a compound and method of treatment which will be active in reducing craving for the abused substance, and which does not exacerbate the

sympathetic response rate caused by the abused substance and which has favourable pharmacodynamic effects.

The compounds are also potentially useful as agents for treating pain disorders, including
5 but not limited to acute and chronic nociceptive, inflammatory and neuropathic pain and migraine.

In another aspect the present invention provides a compound of formula I as claimed in any previous claim for use as a medicament.

10 In a further aspect the present invention provides the use of a compound of formula I in the preparation of a medicament for the treatment or prophylaxis of obesity, psychiatric disorders such as psychotic disorders, anxiety, anxio-depressive disorders, depression, bipolar disorder, ADHD, cognitive disorders, memory disorders, schizophrenia, epilepsy,
15 and related conditions, neurological disorders such as dementia, multiple sclerosis, Parkinson's disease, Huntington's chorea and Alzheimer's disease and pain related disorders, including but not limited to acute and chronic nociceptive, inflammatory and neuropathic pain and migraine, comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof.

20 In a still further aspect the present invention provides a method of treating obesity, psychiatric disorders such as psychotic disorders, anxiety, anxio-depressive disorders, depression, bipolar disorder, ADHD, cognitive disorders, memory disorders, schizophrenia, epilepsy, and related conditions, and neurological disorders such as
25 dementia, multiple sclerosis, Parkinson's disease, Huntington's chorea and Alzheimer's disease and pain related disorders, including but not limited to acute and chronic nociceptive, inflammatory and neuropathic pain and migraine, comprising administering a pharmacologically effective amount of a compound of formula I to a patient in need thereof.

30 The compounds of the present invention are particularly suitable for the treatment of obesity.

In another aspect the present invention provides a method of treating obesity, type II diabetes, Metabolic syndrome and a method of preventing type II diabetes comprising administering a pharmacologically effective amount of a compound of formula I to a
5 patient in need thereof.

Combination Therapy

The compounds of the invention may be combined with another therapeutic agent that is useful in the treatment of disorders associated with the development and progress of
10 atherosclerosis such as hypertension, hyperlipidaemias, dyslipidaemias, diabetes and obesity. For example, a compound of the present invention may be used in combination with a compound that affects thermogenesis, lipolysis, fat absorption, satiety, or gut motility. The compounds of the invention may be combined with another therapeutic agent
that decreases the ratio of LDL:HDL or an agent that causes a decrease in circulating levels
15 of LDL-cholesterol. In patients with diabetes mellitus the compounds of the invention may also be combined with therapeutic agents used to treat complications related to micro-angiopathies.

The compounds of the invention may be used alongside other therapies for the treatment of
20 metabolic syndrome or type 2 diabetes and its associated complications; these include biguanide drugs, insulin (synthetic insulin analogues), oral antihyperglycemics (these are divided into prandial glucose regulators and alpha-glucosidase inhibitors) and PPAR modulating agents.

25 In another aspect of the invention, the compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, may be administered in association with a PPAR modulating agent. PPAR modulating agents include but are not limited to a PPAR alpha and/or gamma agonist, or pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof. Suitable PPAR alpha and/or gamma
30 agonists, pharmaceutically acceptable salts, solvates, solvates of such salts or prodrugs thereof are well known in the art.

In addition the combination of the invention may be used in conjunction with a sulfonylurea. The present invention also includes a compound of the present invention in combination with a cholesterol-lowering agent. The cholesterol-lowering agents referred to in this application include but are not limited to inhibitors of HMG-CoA reductase (3-
5 hydroxy-3-methylglutaryl coenzyme A reductase). Suitably the HMG-CoA reductase inhibitor is a statin.

In the present application, the term "cholesterol-lowering agent" also includes chemical modifications of the HMG-CoA reductase inhibitors, such as esters, prodrugs and
10 metabolites, whether active or inactive.

The present invention also includes a compound of the present invention in combination with an inhibitor of the ileal bile acid transport system (IBAT inhibitor). The present invention also includes a compound of the present invention in combination with a bile
15 acid binding resin.

According to an additional further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a
20 salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration one or more of the following agents selected from:

- a CETP (cholesteryl ester transfer protein) inhibitor;
- a cholesterol absorption antagonist;
- 25 a MTP (microsomal transfer protein) inhibitor ;
- a nicotinic acid derivative, including slow release and combination products;
- a phytosterol compound ;
- probucol;
- an anti-obesity compound, for example orlistat (EP 129,748) and sibutramine (GB
30 2,184,122 and US 4,929,629);
- an antihypertensive compound, for example an angiotensin converting enzyme (ACE) inhibitor, an angiotensin II receptor antagonist, an adrenergic blocker, an alpha

andrenergic blocker, a beta andrenergic blocker, a mixed alpha/beta andrenergic blocker, an andrenergic stimulant, calcium channel blocker, an AT-1 receptor blocker, a saluretic, a diuretic or a vasodilator;

a CB1 antagonist or inverse agonist, for example rimonabant;

5 another melanin concentrating hormone receptor 1 (MCHr1) antagonist;

a PDK inhibitor; or

modulators of nuclear receptors for example LXR, FXR, RXR, and RORalpha;

an SSRI;

a serotonin antagonist;

10 or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

Therefore in an additional feature of the invention, there is provided a method for the
15 treatment of type 2 diabetes and its associated complications in a warm-blooded animal, such as man, in need of such treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate
administration with an effective amount of a compound from one of the other classes of
20 compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

Therefore in an additional feature of the invention, there is provided a method of treating
hyperlipidemic conditions in a warm-blooded animal, such as man, in need of such
25 treatment which comprises administering to said animal an effective amount of a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof in simultaneous, sequential or separate administration with an effective amount of a compound from one of the other classes of compounds described in
this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a
30 salt or a prodrug thereof.

According to a further aspect of the invention there is provided a pharmaceutical composition which comprises a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in association with a pharmaceutically acceptable diluent or carrier.

According to a further aspect of the present invention there is provided a kit comprising a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a first unit dosage form;
- b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof; in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to a further aspect of the present invention there is provided a kit comprising:

- a) a compound of formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, together with a pharmaceutically acceptable diluent or carrier, in a first unit dosage form;
- b) a compound from one of the other classes of compounds described in this combination section or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in a second unit dosage form; and
- c) container means for containing said first and second dosage forms.

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a

prodrug thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of metabolic syndrome or type 2 diabetes and its associated complications in a warm-blooded animal, such as man.

5

According to another feature of the invention there is provided the use of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, and one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, in the manufacture of a medicament for use in the treatment of hyperlipidaemic conditions in a warm-blooded animal, such as man.

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According to a further aspect of the present invention there is provided a combination treatment comprising the administration of an effective amount of a compound of the formula I, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier, with the simultaneous, sequential or separate administration of an effective amount of one of the other compounds described in this combination section, or a pharmaceutically acceptable salt, solvate, solvate of such a salt or a prodrug thereof, optionally together with a pharmaceutically acceptable diluent or carrier to a warm-blooded animal, such as man in need of such therapeutic treatment.

15

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Experimental section

The invention will now be described in more detail with the following examples that are not to be construed as limiting the invention.

25

Abbreviations:

aq.	aqueous
Ac	acetyl
Bu	butyl
tBoc	<i>tert</i> -butyloxycarbonyl
Cbz	benzyloxycarbonyl

30

	CHO	Chinese hamster ovary (cells)
	DCM	methylene chloride, CH ₂ Cl ₂
	DIPEA	N,N-Diisopropylethylamine
	DMA	dimethyl acetamide
5	DMF	N,N-dimethylformamide
	DTT	dithiothreitol
	EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
	EDTA	ethylenediamine tetraacetic acid
	ELS	evaporative light scattering
10	ESI	electrospray ionization
	Et	ethyl
	GDP	guanosine 5'-diphosphate
	GPCR	G-protein coupled receptor
	GTP	guanosine 5'-triphosphate
15	HATU	O-(azabenzotriazol-1-yl)-N, N, N', N'-tetramethyluronium hexafluoro-phosphate
	HEK	human embryotic kidney (cells)
	HEPES	N-2-hydroxyethyl piperazine-N'-2-ethanesulfonic acid
	hERG	human <i>ether-a-go-go</i> related gene (potassium ion channel)
20	HPLC	high performance liquid chromatography
	HOAt	1-Hydroxy-7-azabenzotriazole
	LC	liquid chromatography
	MP-BH(OAc) ₃ :	macroporous polymer bound triacetoxymethylborohydride (available from Argonaut) Typically 2-3meq/g BH
25	MS	mass spectroscopy
	Pol-BH ₃ CN	(polystyrylmethyl)trimethylammonium cyanoborohydride (loading 4.1-4.3 mmol BH ₃ CN/g)
	Pol-CHO	4-benzyloxybenzaldehyde polystyrene (loading ~2.66 mmol CHO/g)
30	PyBroP	Bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
	TBTU	N, N, N', N'-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate
	TEA	triethylamine

	TFA	trifluoroacetic acid
	TFFH	tetramethylfluoroformamidium hexafluorophosphate
	THF	tetrahydrofuran
	TLC	thin layer chromatography
5	Tris	trishydroxymethylaminomethane
	Tween	polyoxyethylene sorbitan monolaurate
	<i>t</i>	tert
	rt.	room temperature
	sat.	saturated
10	br	broad
	bs	broad singlet
	d	doublet
	dd	doublet of doublets
	dt	doublet of triplets
15	m	multiplet
	q	quartet
	s	singlet
	t	triplet

20 General Experimental Procedures

Flash column chromatography employed MERCK normal phase silica gel 60 Å (40-63 µm) or a Biotage Horizon Pioneer® HPFC system equipped with FLASH 12+M or FLASH 25+M or 40+M silica cartridges. Mass spectra were recorded on a Waters Micromass ZQ single quadrupole equipped with a pneumatically assisted electrospray interface (LC-MS).

25 HPLC analyses were performed on a Gynkotek P580 HPG, gradient pump with a Gynkotek UVD 170S UV-Vis detector. Column: Chromolith Performance RP-18e, 4.6 x 100 mm, Mobile phase A: Acetonitrile, Mobile phase B: 0.1% TFA (aq), Flow: 3 ml/min, Injection volume: 20 µl, Detection: 254 and 275 nm.

30 Purifications were performed on a semi preparative HPLC, Shimadzu LC-8A, Shimadzu SPD-10A UV-vis. detector equipped with a Waters X-terra® Prep MS C₁₈ Column, 250 mm x 50 mm (10 µm) or on a Waters Prep LC 2000 with UV-detection, equipped with a

Kromasil 10 μ m C8 250 mm x 20 mm column, or on a semi preparative HPLC, Shimadzu LC-8A, Shimadzu SPD-10A UV-vis.-detector equipped with a Waters Symmetry® 100 mm x 19 mm C18 5 μ m column.

Automated Preparative HPLC was done using a Waters Fraction Lynx system equipped
5 with UV, ELS and MS detection and an Ace C8 5 μ 10 cm x 21,2 id column. The mobile phase was A: 95% CH₃CN and B: 5% CH₃CN + 95% 0,1 M NH₄OAc with a gradient from 100% B to 100% A in 10 minutes at 25 mL/min flow rate.

¹H NMR and ¹³C NMR spectra were obtained at 298 K on a Varian Unity Plus 400 MHz, or a Varian Inova 500 MHz or a Varian Unity Plus 600 MHz or a Bruker Avance 300 MHz
10 or Varian Gemini 2000 300 MHz. Chemical shifts are given in ppm with the solvent residual peak as internal standard: CDCl₃ δ _H 7.26, δ _C 77.2; MeOH-*d*₄ δ _H 3.31, δ _C 49.0; DMSO-*d*₆ δ _H 2.50; δ _C 39.5 ppm.

Microwave heating was performed using single node heating in a Smith Creator from Personal Chemistry, Uppsala, Sweden.

15 Chemical names (IUPAC) were generated using the software ACD/ Name version 7.00.

Names/reference numbers of starting materials (CAS no), either commercially available or prepared according to literature procedures.

Pyrrol-3-aldehyde, 7126-39-8; 2-chloro-5-(trifluoromethyl)-pyridine, 52334-81-3; 2,5-dimethoxy-3-tetrahydrofurancarboxaldehyde, 50634-05-4; 4-aminobenzotrifluoride, 455-
20 14-1; 5-trifluoromethyl-pyridine-2-ylamine, 74784-70-6; *tert*-butyl piperidin-4-ylcarbamate 73874-95-0; bis(4-fluorophenyl)methanone, 345-92-6; [1-(*tert*-butoxycarbonyl)piperidin-4-yl]acetic acid, 157688-46-5; (3,4-difluorobenzyl)amine, 72235-53-1; 1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid, 84358-13-4; diphenylacetic acid, 117-34-0; 1-isocyanato-4-(trifluoromethoxy)benzene, 35037-73-1;
25 2,4-dichloro-1-isocyanatobenzene, 2612-57-9; 1-isocyanatonaphthalene, 86-84-0; 1-fluoro-3-(isocyanatomethyl)benzene, 102422-56-0; 4-fluoroaniline, 371-40-4; 1-bromo-4-fluorobenzene, 460-00-4; *tert*-butyl 4-aminopiperidine-1-carboxylate, 87120-72-7; *tert*-butyl piperidin-4-ylcarbamate, 73874-95-0; ethyl piperidine-4-carboxylate, 1126-09-6; (4-fluorophenyl)amine, 371-40-4; 1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl]acetic acid, 175526-
30 97-3; methyl(phenyl)carbamic chloride, 4285-42-1; 1-(1,3-benzothiazol-2-yl)methanamine hydrochloride, 29198-41-2; 2-(3-fluorophenyl)pyrrolidine, 298690-72-9; 2-(1*H*-imidazol-1-yl)-1-phenylethanamine 24169-72-0; (3-fluorobenzyl)methylamine, 90389-84-7; 4-

azetidin-3-ylthiomorpholine 1,1-dioxide, 780732-40-3; 4-aminobutan-2-ol, 39884-48-5; (2*S*)-2-amino-2-phenylethanol, 7568-92-5; 2-pyrrolidin-2-yl-1,3-benzothiazole, 359804-21-0; 3-(pyrrolidin-2-ylmethyl)pyridine, 106366-28-3; 4-chloro-2-methoxybenzoic acid, 57479-70-6; [1-(*tert*-butoxycarbonyl)piperidin-4-yl]acetic acid, 157688-46-5; 2-piperidin-2-ylethanol, 1484-84-0; 3-[(4-fluorobenzyl)amino]propan-1-ol, 161798-73-8; 1-amino-3-phenoxypropan-2-ol hydrochloride, 86809-29-2; 1-(aminomethyl)cyclohexanol hydrochloride, 19968-85-5; methyl 6-methoxynicotinate, 26218-80-4; 2-methyl-1*H*-imidazole, 693-98-1; 2-bromo-1-phenylethanone, 70-11-1.

5-chloro-6-methoxynicotinic acid (cat. no. 111823) was purchased from Asymchem Laboratories, Inc., Durham, NC, USA.

Preparation of Intermediates

Example A

15 1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrole-3-carbaldehyde

To a solution of 2,5-dimethoxy-3-tetrahydrofurancarboxaldehyde (8.0 g, 49.9 mmol) in acetic acid (120 mL) was added 4-aminobenzotrifluoride (8.05 g, 49.9 mmol) and the mixture was heated at reflux under an atmosphere of nitrogen until HPLC indicated that starting material was consumed. The reaction mixture was concentrated and the residue was dissolved in EtOAc (500 mL) and washed with 2M NaOH (aq) (100 mL) and brine. The organic phase was dried (Na₂SO₄) and then evaporated to dryness. The residue was purified on SiO₂ eluted with DCM and finally DCM:MeOH (98:2) to give 8.56 g (72%) of the title compound (94% pure, HPLC purity).

¹H NMR (CDCl₃) δ 9.87 (s, 1H), 7.76 (m, 2H), 7.72 (m, 1H), 7.55 (m, 2H), 7.14 (m, 1H), 6.84 (m, 1H).

¹³C NMR (CDCl₃) δ 185.5, 142.2, 129.4 (q, *J* = 33 Hz), 129.0, 127.4 (q, *J* = 4 Hz), 126.8, 123.8 (q, *J* = 272 Hz), 122.1, 121.1, 110.5.

MS (ESI) 240 (M + 1H⁺).

30 Example B

1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrole-3-carbaldehyde

Pyrrol-3-aldehyde (4.0 g, 42.1 mmol) in THF (100 mL) was added to NaH (1.5 g, 63.2 mmol) in THF (30 mL) and the mixture was stirred at r.t. under an atmosphere of nitrogen until no more H₂ was generated. 2-chloro-5-(trifluoromethyl)-pyridine (8.4 g, 46.3 mmol) was added and the mixture was stirred at 50 °C under an atmosphere of nitrogen for 75 minutes. The solvent was removed by evaporation and water was added to the resulting solid. The aq. layer was washed with DCM and the organic layer was separated and dried over Na₂SO₄. The resulting brown residue was purified twice on a SiO₂ column eluting first with pure DCM and then with Heptane:EtOAc (3:1). The resulting yellow solid was washed with cold Et₂O to give 5.73 g (57%) of the title compound as a solid.

MS (ESI) 241 (M + H⁺).

Example C

1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl}piperidin-4-amine dihydrochloride

a) *tert*-butyl-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl}-piperidin-4-yl]-carbamate

1-[4-(trifluoromethyl)phenyl]-1H-pyrrole-3-carbaldehyde (4.054 g, 16.95 mmol) and *tert*-butyl piperidin-4-ylcarbamate, (3.564 g, 17.80 mmol) was suspended in DCM (35 mL). NaBH(OAc)₃ (7.184 g, 33.90 mmol) was added and stirred overnight at rt. The reaction mixture was quenched with sat. NH₄Cl aq. solution (30 mL), extracted with DCM (3 x 40 mL), washed with brine (30 mL), dried with Na₂SO₄ and purified with Biotage Horizon Pioneer® HPFS using a silica cartridge and eluted with EtOAc:MeOH:TEA (gradient from 100:0:0 to 100:5:0.1) to give 6.12 g (85%) of the title compound as a solid.

¹HNMR (MeOD-d₄) δ 7.77 (d, 2H), 7.71 (d, 2H), 7.51 (s, 1H), 7.40 (t, 1H), 6.48 (m, 1H), 4.08 (s, 2H), 3.55-3.58 (m, 1H), 3.38 (d, 2H), 2.84 (t, 2H), 2.08 (m, 2H), 1.72 (m, 2H), 1.43 (s, 9H).

MS (ESI) 424.3 (M + 1H⁺).

b) **1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl}piperidin-4-amine dihydrochloride**

tert-butyl-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]
carbamate (6.119 g, 14.45 mmol) was dissolved in HCl 4 M in 1,4-dioxane (35 mL) and
stirred at rt. for 1.5 hours. Et₂O (10 mL) was added to the suspension which was stirred for
1.5 hours. The precipitate was filtered off and was washed with Et₂O (200 mL) and was
5 then dried at reduced pressure over night to give 4.98 g (87%) of the title compound as a
solid.

¹H NMR (MeOD-*d*₄) δ 7.77 (m, 4H), 7.63 (s, 1H), 7.40 (t, 1H), 6.56 (s, 1H), 4.28 (s, 2H),
3.65-3.69 (m, 2H), 3.49 (m, 1H), 3.16 (t, 2H), 2.30 (m, 2H), 1.99-2.10 (m, 2H).
MS (ESI) 325.2 (M + 1H⁺).

Working Examples

Example 1

2,2-diphenyl-*N*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-
15 yl]acetamide

1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-amine
dihydrochloride (0.100 g, 0.25 mmol), diphenylacetic acid (0.080 g, 0.38 mmol),
potassium carbonate (0.139 g, 1.00 mmol) and EDC (0.073 g, 0.38 mmol) was dissolved in
DCM:H₂O 1:1 (2 mL) and stirred at 18 hours at room temperature. The organic phase was
20 concentrated and purified with Biotage Horizon Pioneer® HPFS using a silica cartridge
with gradient elution, EtOAc and EtOAc:MeOH:TEA (100:2:0.2) to give the title
compound in 0.085 g (65%).

¹H NMR (CD₃OD) δ 7.69 (d, 2H, *J*=9.3 Hz), 7.60 (d, 2H, *J*=9.3Hz), 7.16-7.24 (m, 12H),
6.32 (m, 1H), 4.93 (s, 1H), 3.68 (m, 1H), 3.43 (s, 2H), 2.91 (d, 2H, *J*=11.1Hz), 2.10 (t, 2H,
25 *J*=11.7Hz), 1.84 (d, 2H, *J*=11.7), 1.51 (m, 2H).

¹³C NMR (CDCl₃) δ 171.4, 143.2, 139.8, 129.1, 128.9, 127.8 (q, *J*=3.8Hz), 127.4, 127.3
(q, *J*=33.1Hz), 124.1 (q, *J*=271.8Hz), 123.9, 119.1, 118.3, 59.4, 55.4, 52.2, 46.9, 32.2.

MS (ESI+) 518.4(M + 1H⁺), MS (ESI-) 516.2(M - 1H⁺).

Example 2

N-(3,4-difluorobenzyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-
yl}methyl)piperidin-4-yl]acetamide

a) *tert*-butyl-4-{2-[(3,4-difluorobenzyl)amino]-2-oxoethyl}piperidine-1-carboxylate

[1-(*tert*-butoxycarbonyl)piperidin-4-yl]acetic acid (0.200 g, 0.82 mmol) and EDC (0.205 g, 1.0 mmol) was dissolved in DCM (6 mL). (3,4-Difluorobenzyl)amine (0.153 g, 1.0 mmol) was added the solution and stirred for 5 hours at room temperature. 10% Na₂CO₃(aq.) (4 mL) was added and the phases were separated on a phase separator, concentrated and purified with Biotage Horizon Pioneer® HPFS using a silica cartridge with gradient elution n-Heptane / EtOAc:MeOH:TEA (100:2:0.2) to give the title compound in 0.161 g (53%).

¹H NMR (CD₃OD) δ 7.30-7.12 (m, 2H), 7.21-6.98 (m, 1H), 4.32 (s, 2H), 4.04 (s, 1H), 4.01 (s, 1H), 2.74 (bs, 2H), 2.16 (d, 2H, J=6.9 Hz), 1.94 (m, 1H), 1.65 (d, 2H, J=12.1 Hz), 1.43 (s, 9H), 1.11 (m, 2H).

b) *N*-(3,4-difluorobenzyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide

tert-butyl 4-{2-[(3,4-difluorobenzyl)amino]-2-oxoethyl}piperidine-1-carboxylate (0.161 g, 0.44 mmol) was dissolved in 4M HCl in 1,4-dioxane (10 mL) and stirred for 1.5 hours at room temperature. Added Et₂O (10 mL). The precipitate was filtered off, washed with Et₂O and dried. The precipitate, 1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrole-3-carbaldehyde (0.115 g, 0.48 mmol), NaBH(OAc)₃ (0.185 g, 0.87 mmol) and DIPEA (0.056 g, 0.44 mmol) was dissolved in DCM (8 mL) and stirred for 5 hours at room temperature. Added sat. NH₄Cl(aq.) (5 mL) and separated on phase separator, concentrated and purified with Biotage Horizon Pioneer® HPFS using a silica cartridge with EtOAc:MeOH:TEA (100:2:0.2) to give the title compound in 0.125 g (58%).

¹H NMR (CDCl₃) δ 7.63 (d, 2H, J=9.2Hz), 7.42 (d, 2H, J=9.2Hz), 7.01-7.09 (m, 4H), 6.94 (m, 1H), 6.30 (m, 1H), 6.17 (t, 1H, J=5.8Hz), 4.33 (d, 2H, J=6.0Hz), 3.41 (s, 2H), 2.94 (d, 2H, J=11.0), 2.10 (d, 2H, J=7.7Hz), 1.96 (m, 2H), 1.82 (m, 1H), 1.68 (d, 2H, J=11.6), 1.28 (m, 2H).

¹³C NMR (CDCl₃) δ 172.3, 151.4 (dd, J=13.6Hz, J=68.2Hz), 148.9 (dd, J=12.9Hz, J=68.2Hz), 143.2, 135.9 (dd, J=3.92Hz), 127.3 (q, J=32.6Hz), 127.1 (q, J=3.9Hz), 124.3 (q, J=273.2Hz), 123.7, 123.8 (dd, J=3.8Hz), 129.6, 119.0, 118.4, 117.6 (d, J=17.6Hz), 116.8 (d, J=17.6Hz), 113.4, 55.7, 53.6, 43.9, 42.7, 33.5, 32.4.

MS (ESI+) 492.3(M + 1H⁺), MS (ESI-) 490.2(M - 1H⁺).

Example 3

N-(2-phenylethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide

a) *tert*-butyl 4-{{(2-phenylethyl)amino}carbonyl}piperidine-1-carboxylate

1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (0.500 g, 2.18 mmol) and EDC (0.543 g, 2.84 mmol) was dissolved in DCM (10 mL). (2-Phenylethyl)amine (0.344 g, 2.84 mmol), DCM (20 mL) was added and the solution was stirred for 5 hours at room temperature. 10% Na₂CO₃(aq.) (20 mL) was added and the phases were separated on a phase separator, concentrated and purified with Biotage Horizon Pioneer® HPFS using a silica cartridge with gradient elution n-Heptane / EtOAc:MeOH:TEA (100:2:0.2) to give the title compound in 0.244 g (37%).

¹H NMR (CD₃OD) δ 7.22 (m, 5H), 4.82 (bs, 1H), 4.05 (m, 2H), 3.39 (bs 2H), 2.77 (bs, 4H), 2.29 (bs, 1H) 1.64 (bs, 2H), 1.44 (m, 10H).

b) *N*-(2-phenylethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide

tert-butyl 4-{{(2-phenylethyl)amino}carbonyl}piperidine-1-carboxylate (0.244 g, 0.73 mmol) was dissolved in 4M HCl in 1,4-dioxane (10 mL) and stirred for 1.5 hours at room temperature and Et₂O 10 mL) was added. The precipitate was filtered off, washed with diethyl ether and dried. The precipitate, 1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrole-3-carbaldehyde (0.193 g, 0.81 mmol), NaBH(OAc)₃ (0.311 g, 1.47 mmol) and DIPEA (0.095 g, 0.73 mmol) was dissolved in DCM (8 mL) and stirred for 5 hours at room temperature. Saturated NH₄Cl (aq.) (5 mL) was added and the phases were separated on a phase separator, concentrated and purified with Biotage Horizon Pioneer® HPFS using a silica cartridge with EtOAc:MeOH:TEA (100:2:0.2) to give the title compound in 0.228 g (68%).

¹H NMR (CDCl₃) δ 7.63 (d, 2H, *J*=8.8Hz), 7.42 (d, 2H, *J*=8.8Hz), 7.21 (m, 5H), 7.03 (m, 2H), 6.30 (s, 1H), 5.78 (m, 1H), 3.49 (q, 2H, *J*=6.20), 3.42 (s, 2H) 2.99 (d, 2H, *J*=12.4) 2.79 (t, 2H, *J*=6.9), 1.90-2.10 (m, 3H), 1.67-1.82(m, 4H).

^{13}H NMR (CDCl_3) δ 175.3, 143.2, 139.2, 124.3 (q, $J=271\text{Hz}$), 129.0, 128.8, 127.3 (q, $J=32.4\text{Hz}$), 127.1 (q, $J=3.7\text{Hz}$), 126.7, 123.7, 119.6, 119.1, 118.3, 113.2, 55.6, 53.2, 43.6, 40.7, 35.9, 29.2.

5 **Example 4**

N-[bis(4-fluorophenyl)methyl]-2-[1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl)methyl]piperidin-4-yl]acetamide

a) [bis(4-fluorophenyl)methyl]amine

10 bis-(4-fluorophenyl)methanone (3.0 g, 13.7 mmol) was added to methanol (30 mL), and ammonium acetate (7.4 g, 96.2 mmol) was added. The mixture was stirred for 0.5 hours. NaBH_3CN (0.95 g, 15.1 mmol) was added and the mixture was stirred over night. Further NaBH_3CN (0.5 g, 7.95 mmol) was added and the mixture was refluxed over night. Evaporated, added 1% Na_2CO_3 (aq) solution (40 mL), extracted with ethylacetate (3x60
15 mL). The organic phases was washed with brine (40 mL), dried (Na_2SO_4) and purified with Biotage Horizon Pioneer® HPFS using a silica cartridge with gradient elution EtOAc / *n*-Heptane to give the title compound in 1.155 g (38%).

^1H NMR (CDCl_3) δ 7.24 (m, 4H), 7.00 (m, 4H), 6.16 (s, 2H), 5.26 (s, 1H).

20 b) *tert*-butyl-4-(2-([bis(4-fluorophenyl)methyl]amino)-2-oxoethyl)piperidine-1-carboxylate

[1-(*tert*-butoxycarbonyl)piperidin-4-yl]acetic acid (0.500 g, 2.06 mmol), [bis(4-fluorophenyl)methyl]amine (0.496 g, 2.26 mmol) and EDC (0.433 g, 2.26 mmol) was added to DCM (20 mL) and stirred for 6 hours at room temperature. The mixture was
25 concentrated and purified with Biotage Horizon Pioneer® HPFS using a silica cartridge with gradient elution EtOAc:MeOH:TEA (100:2:0.2) / *n*-Heptane to give the title compound in 0.455 g (50%).

^1H NMR (CDCl_3) δ 7.13 (m, 4H), 6.95 (m, 4H), 6.8 (d, 1H), 6.18 (d, 1H), 3.96 (d, 2H), 2.61 (bs, 2H), 2.10 (m, 2H), 1.93 (m, 1H), 1.58 (d, 2H), 1.40 (s, 9H), 1.03 (m, 2H).

30

c) *N*-[bis(4-fluorophenyl)methyl]-2-piperidin-4-ylacetamide hydrochloride

tert-butyl-4-(2-([bis(4-fluorophenyl)methyl]amino)-2-oxoethyl)piperidine-1-carboxylate (0.455 g, 1.02 mmol) was dissolved in a 4 M HCl solution in 1,4-dioxane and was stirred for 2 hours at room temperature, whereafter Et₂O (25 mL) was added. The precipitate was filtered off and washed with Et₂O (30 mL) and dried *in vacuo* to give the title compound in
 5 0.336 g (86%).

¹H NMR (CD₃OD) δ 7.25 (m, 4H), 7.06 (m, 4H), 6.18 (m, 1H), 3.35 (d, 2H), 2.97 (m, 2H), 2.30 (d, 2H), 2.08 (m, 1H), 1.90 (d, 2H), 1.45 (bq, 2H).
 MS (ESI+) 345.2(M + 1H⁺), MS (ESI-) 343.1(M - 1H⁺).

10 d) ***N*-[bis(4-fluorophenyl)methyl]-2-[1-([1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl)methyl]piperidin-4-yl]acetamide**

N-[bis(4-fluorophenyl)methyl]-2-piperidin-4-ylacetamide hydrochloride (0.193 g, 0.51 mmol), 1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrole-3-carbaldehyde (0.134 g, 0.56 mmol), NaBH(OAc)₃ (0.118 g, 0.56 mmol) and DIPEA (0.065 g, 0.51 mmol) were added
 15 to DCM (5 mL) and stirred at 18 hours at room temperature. Additional NaBH(OAc)₃ (0.100 g, 0.27 mmol) and DCM (10 mL) was added and the mixture was stirred for 6 hours. Saturated NH₄Cl (aq) (15 mL) was added. The organic phase was separated, concentrated and was purified with Biotage Horizon Pioneer® HPFS using a silica cartridge with gradient elution EtOAc:MeOH:TEA (100:5:0.5) / *n*-Heptane to give the title
 20 compound in 0.175 g (60%).

¹H NMR (CDCl₃) δ 8.62 (bs, 1H), 7.90 (m, 1H), 7.47 (m, 1H), 7.41 (m, 1H), 7.32 (d, 1H), 7.13 (m, 4H), 6.97 (m, 4H), 6.32 (m, 1H), 6.28 (d, 1H), 6.17 (d, 1H), 3.40 (s, 2H), 2.92 (m, 2H), 2.12 (d, 2H), 1.94 (m, 2H), 1.80 (m, 1H), 1.65 (bd, 2H), 1.28 (m, 2H).

¹³CNMR (CDCl₃): δ 171.4, 162.1 (d, *J*=242), 153.4, 146.4 (q, *J*=4.2), 137.4 (d, *J*=3.1),
 25 136.0 (q, *J*=3.3), 129.2 (d, *J*=7.6), 124.7, 123.8 (q, *J*=272), 122.7 (q, *J*=33), 118.5, 117.6, 115.8 (d, *J*=22), 114.3, 110.5, 55.8, 55.7, 53.6, 43.9, 33.6, 32.4

MS (ESI+) 569.3(M + 1H⁺), MS (ESI-) 567.2(M - 1H⁺).

Example 5

30 ***N*-[4-(bifluoromethoxy)phenyl]-*N'*-[1-([1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl]piperidin-4-yl]urea**

1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-amine dihydrochloride (0.050 g, 0.126 mmol), 1-isocyanato-4-(trifluoromethoxy)benzene (0.038 g, 0.19 mmol) and DIPEA (0.040 g, 0.31 mmol) were dissolved in dry THF (4 mL) and stirred for 18 hours at room temperature. The organic phase was concentrated and purified with prep. HPLC to give the title compound in 0.034 g (51%).

¹H NMR (CD₃OD) δ 7.73 (d, 2H, *J*=9.6Hz), 7.65 (d, 2H, *J*=Hz), 7.42 (d, 2H, *J*=8.5), 7.33 (s, 1H), 7.30 (s, 1H), 7.12 (d, 2H, *J*=9.6Hz), 6.39 (s, 1H), 3.65 (m, 3H), 3.09 (d, 2H, *J*=11.9), 2.45 (t, 2H, *J*=11.1), 2.00(m, 2H), 1.6 (m, 2H).

MS (ESI+) 527.4(M + 1H⁺), MS (ESI-) 525.1(M - 1H⁺).

Example 6

N-(2,4-dichlorophenyl)-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea

1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-amine dihydrochloride (0.100 g, 0.25 mmol), 2,4-dichloro-1-isocyanatobenzene (0.063 g, 0.33 mmol) and DIPEA (0.075 g, 0.69 mmol) were dissolved in dry THF (4 mL) and stirred 18 hours at room temperature. The organic phase was concentrated and purified with Biotage Horizon Pioneer® HPFS using a silica cartridge with EtOAc:MeOH:TEA (100:5:0.1) to give the title compound in 0.087 g (67%).

¹H NMR (CD₃OD) δ 8.04 (d, 1H, *J*=9.9Hz), 7.73 (d, 2H, *J*=8.6Hz), 7.66 (d, 2H, *J*=8.6Hz), 7.39 (m, 1H), 7.28 (m, 2H), 7.22 (m, 1H), 6.36 (m, 1H), 3.65 (m, 1H), 3.5 (s, 2H), 2.93 (m, 2H), 2.24 (t, 2H, *J*=10.5Hz), 1.97 (m, 2H), 1.53 (m, 2H).

MS (ESI+) 512(M + 1H⁺), MS (ESI-).

Example 7

N-1-naphthyl-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea

1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-amine dihydrochloride (0.050 g, 0.13 mmol), 1-isocyanatonaphthalene (0.031 g, 0.19 mmol), and DIPEA (0.040 g, 0.31 mmol) were dissolved in dry THF (4 mL) and stirred 18 hours at room temperature. The organic phase was concentrated and purified with Biotage Horizon

Pioneer® HPFS using a silica cartridge with EtOAc:MeOH:TEA (100:5:0.1) to give the title compound in 0.030 g (46%).

¹H NMR (CD₃OD) δ 7.97 (d, 1H, *J*=8.7Hz), 7.85 (d, 1H, *J*=8.7), 7.62-7.75 (m, 6H), 7.39-7.53 (m, 3H), 7.30 (m, 2H), 6.38 (m, 1H), 3.68 (m, 1H), 3.59 (m, 2H), 3.03 (d, 2H, *J*=10.8Hz), 2.34 (t, 2H, *J*=10.8Hz), 2.02 (d, 2H, *J*=13.1Hz), 1.59 (m, 2H).

Example 8

N-(3-fluorobenzyl)-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea

1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-amine dihydrochloride (0.163 g, 0.41 mmol), 1-fluoro-3-(isocyanatomethyl)benzene (0.092 g, 0.61 mmol) and DIPEA (0.130 g, 1.00 mmol) were dissolved in THF (5 mL) and stirred 18 hours at room temperature. The organic phase was concentrated and purified with Biotage Horizon Pioneer® HPFS using a silica cartridge with EtOAc:MeOH:TEA (100:5:0.1) to give the title compound in 0.118 g (61%).

¹H NMR (CD₃OD) δ 7.71 (d, 2H), 7.64 (d, 2H), 7.26-7.31 (m, 3H), 6.92-7.07 (m, 3H), 6.35 (m, 1H) 4.29 (s, 2H), 3.52 (m, 1H), 3.48 (s, 2H), 2.93 (d, 2H) 2.18 (t, 2H), 1.89 (m, 2H), 1.48 (m, 2H).

MS (ESI+) 475.4(M + 1H⁺), MS (ESI-) 473.1(M - 1H⁺).

Example 9

N,N-bis(4-fluorophenyl)-*N'*-[1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea

a) *N,N*-bis-(4-fluoro-phenyl)-acetamide

Acetic anhydride (2.76 g, 27 mmol) was added dropwise to 4-fluoroaniline (3.0 g, 27 mmol) under an atmosphere of nitrogen. The mixture solidified during the addition. 1-Bromo-4-fluorobenzene (4.78 g, 27 mmol) was added to the mixture. Potassium carbonate (5.3 g, 38 mmol) and copper iodide (500 mg) was added and the mixture was heated to 240 °C and the mixture was stirred for 4 h. The mixture was diluted first with xylene and then, after cooling to room temperature, with DCM. The organic layers were combined and the

solvent was removed. Purification on silica gel eluting with DCM:MeOH (99:1→ 9:1) gave 3.0 g (46% yield) of the title compound.

b) bis-(4-fluoro-phenyl)-amine

5 N,N-bis-(4-fluoro-phenyl)-acetamide (2.23 g, 9.2 mmol) in MeOH (30 mL) and HCl (10% aq, 30 mL) was refluxed at 100 °C over night. LC-MS indicated presence of the title compound in the mixture. The mixture was made basic by addition of aq. NaOH (15%). The methanol was removed by evaporation and the aq. layer was extracted with CHCl₃. The organic layer was separated and dried over Na₂SO₄. The solvent was removed by
10 evaporation to give 1.70 g (90%) of the title compound as an oil.

c) 4-[3,3-bis-(4-fluoro-phenyl)-ureido]-piperidine-1-carboxylic acid tert-butyl ester

To a solution of triphosgene (5.1 g, 17.2 mmol) in THF (60 mL), *tert*-butyl 4-aminopiperidine-1-carboxylate (1.72 g, 8.58 mmol) in THF (10 mL) and triethylamine
15 (1.73 g, 17.2 mmol) was added drop wise over 35 min. at -5 °C. the mixture was stirred for 0.5 h and then refluxed for 1 h. The thick white solution was then filtered and the filtrate was concentrated to ca 10 mL. 50 mL THF was added to the solution and the evaporation procedure was repeated 3 times. The solution was then added drop wise to a solution of bis-(4-fluoro-phenyl)-amine (1.2 g, 5.84 mmol) in THF (30 mL) under an
20 atmosphere of nitrogen. The mixture was stirred at room temperature over night and then refluxed at 90 °C for 4 h. The solvent was removed by evaporation and the residue was washed with aq. NaOH (15%) and DCM. The organic layer was separated and the solvent was removed. Purification on silica gel eluting first with Heptane:EtOAc (4:1) and then with pure MeOH gave small amount of title compound (LC-MS analysis) which was taken
25 to the next step without any further purification.

d) 1,1-bis-(4-fluoro-phenyl)-3-piperidin-4-yl-urea

TFA (3 mL) was added to a solution of the collected 4-[3,3-Bis-(4-fluoro-phenyl)-ureido]-piperidine-1-carboxylic acid *tert*-butyl ester in DCM (10 mL) and the mixture was stirred
30 until LC-MS indicated the completion of the reaction. Aq. 2 N NaOH was added and the mixture was stirred. The organic layer was separated and the solvent was removed.

Purification on silica gel eluting with DCM:MeOH (9:1 → 7:3 containing 0.1% ammonia (25% aq. solution)) gave 136 mg of a brown residue which was dissolved in EtOAc and washed with sat. aq. K₂CO₃. The organic layer was separated and evaporated to dryness to give 126 mg (6.5% overall yield) of the title compound.

5

e) *N,N*-bis(4-fluorophenyl)-*N'*-[1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea

N,N-bis(4-fluorophenyl)-*N'*-piperidin-4-ylurea (126 mg, 0.38 mmol) and 1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrole-3-carbaldehyde (1.2 eq) were dissolved in DCM (7.5 ml) in a 16ml vial and stirred for 10 minutes. MP-BH(OAc)₃ (2.5eq) was added and the vial loosely sealed with a cap and stirred at rt for 2h. The reaction was filtered washing with MeOH (2 ml) and the filtrate evaporated in vacuo to yield a yellow oil. Flash chromatography on the Biotage 9g column using gradient EtOAc:MeOH:TEA (100:5:0.5) 10-100% over 540 mL against EtOAc gave the product as a foam (157 mg, 74%).

¹HNMR (CDCl₃) δ 8.6 (s, 1H), 7.90 (d, 1H), 7.45 (d, 2H), 7.35 (d, 1H), 7.2 (t, 4H), 7.0 (t, 4H) 6.3 (s, 1H), 4.40 (d, 1H), 3.7 (m, 1H), 3.40 (s, 2H), 2.80 (d, 2H), 2.20 (t, 2H), 1.90 (d, 2H), 1.40 (m, 2H).

¹³CNMR (CDCl₃): δ 160.9 (d, *J*=247), 155.6, 153.4, 146.3 (q, *J*=3.3), 138.8 (d, *J*=3.3), 136.0 (q, *J*=3.3), 129.1 (d, *J*=8.3), 123.8 (q, *J*=271), 123.7, 122.8 (q, *J*=35), 118.7, 117.8, 116.5 (d, *J*=22.3), 114.1, 110.5, 55.0, 51.9, 47.9, 32.3.

20

MS (ESI+) 556.4 (M+H⁺)

Example 10

***N*-(diphenylmethyl)-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea**

25

a) *tert*-butyl-[1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]carbamate

1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrole-3-carbaldehyde (1.500 g, 6.24 mmol), *tert*-butyl piperidin-4-ylcarbamate (1.313 g, 6.55 mmol) and sodium triacetoxyborohydride (2.647 g, 12.50 mmol) were dissolved in DCM (35 mL) and stirred over night at room temperature. Saturated aq. NH₄Cl was added to the reaction mixture and the organic phase

30

was extracted with DCM (3*40 mL), dried, evaporated and purified with Biotage Horizon Pioneer® HPFS using a silica cartridge with EtOAc:MeOH:TEA (100:2:0.2) to give the title compound in 1.752 g as a solid (66 %).

¹H NMR (CD₃OD) δ 8.71 (s, 1H), 8.14 (d, 1H), 7.63-7.72 (m, 3H), 6.40 (m, 1H), 3.49 (s, 2H), 3.34-3.39 (m, 1H), 2.98 (s, 1H), 2.96 (s, 1H), 2.17 (t, 2H), 1.90 (s, 1H), 1.87 (s, 1H), 1.50-1.57 (m, 2H), 1.46 (s, 9H).

b) 1-((1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrrol-3-yl)methyl)piperidin-4-amine trihydrochloride

tert-butyl-[1-((1-[5-(trifluoromethyl)pyridin-2-yl]-1H-pyrrol-3-yl)methyl)piperidin-4-yl]carbamate (1.752 g, 4.13 mmol) was dissolved in 4M HCl in 1,4-dioxane (50 mL) and stirred for 4 hours. Diethyl ether (50 mL) was added and the resulting precipitate filtered and washed with diethyl ether (100 mL) and dried *in vacuo* to give the title compound in 1.576 g as a solid (88 %).

¹H NMR (CD₃OD) δ 8.75 (s, 1H), 8.19-8.22 (m, 1H), 8.00 (s, 1H), 7.77-7.82 (m, 2H), 6.58 (m, 1H), 4.29 (s, 2H), 3.67 (s, 2H), 3.49 (m, 1H), 3.16 (t, 2H), 2.28 (m, 2H), 2.03 (q, 2H).

c) N-(diphenylmethyl)-N'-[1-((1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl)piperidin-4-yl]urea

1-((1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl)piperidin-4-amine dihydrochloride (0.090 g, 0.23 mmol), 1,1'-(isocyanatomethylene)dibenzene (0.057 g, 0.27 mmol) and DIPEA (0.088 g, 0.68 mmol) were dissolved in THF (7 mL) and stirred at room temperature for 24 h. The organic phase was concentrated *in vacuo* and purified with Biotage Horizon Pioneer® HPFS using a silica cartridge with a gradient elution of EtOAc:MeOH:TEA (100:10:1) in EtOAc to give the title compound as a solid 0.112 g (93%).

¹H NMR (CD₃OD) δ 7.69 (d, 2H), δ 7.53 (d, 2H), δ 7.2 – 7.35 (m, 10H), δ 7.14 (m, 2H), δ 6.35 (s, 1H), δ 6.00 (s, 1H), δ 3.56 (t, 1H), δ 3.47 (s, 2H), δ 2.91 (d, 2H), δ 2.16 (t, 2H), δ 1.92 (d, 2H), δ 1.44 (q, 2H).

^{13}C NMR (CD_3OD) δ 158.2, 143.2, 143.0, 128.5, 127.3, 127.1, δ 127.0 (q, $J=33$), δ 126.9 (q, $J=4$), δ 124.3 (q, $J=270$), δ 122.0, 119.6, 119.3, 118.9, 113.2, 57.7, 55.1, 52.1, 46.8, 32.2.

MS (ESI+) 533.2 ($\text{M} + 1\text{H}^+$), MS (ESI-) 591.2 ($\text{M} - 1\text{H}^+$).

Example 11

N-[bis(4-fluorophenyl)methyl]-2-[1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl)methyl}pyrrolidin-3-yl]acetamide

a) *tert*-butyl 3-(2-([bis(4-fluorophenyl)methyl]amino)-2-oxoethyl)pyrrolidine-1-carboxylate

To [1-(*tert*-butoxycarbonyl)pyrrolidin-3-yl]acetic acid (100 mg, 0.436 mmol) dissolved in DCM (7ml) was added sequentially HOAt (0.436 mmol) and EDC.HCl (0.436mmol) and the mixture was stirred for 5h. [Bis(4-fluorophenyl)methyl]amine (105 mg, 0.480mmol) was then added and the reaction stirred at ambient temperature for 18 hours. The solvent was reduced to about 1 ml and loaded onto 9g biotage flash silica column and eluted with EtOAc and Heptane 20%-70% over 540ml, to provide the title compound as an oil (146 mg, 78% yield).

MS (ESI+) 375.2 ($\text{M} - \text{tBu} + \text{H}^+$), 431.2 ($\text{M} + 1\text{H}^+$); MS (ESI-) 429.1 ($\text{M} - 1\text{H}^+$).

b) *N*-[bis(4-fluorophenyl)methyl]-2-[1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl)methyl}pyrrolidin-3-yl]acetamide

To *tert*-butyl 3-(2-([bis(4-fluorophenyl)methyl]amino)-2-oxoethyl)pyrrolidine-1-carboxylate (146 mg, 0.339 mmol) was added 4M HCl in Dioxane (10 ml) and the mixture stirred for 2 hours. The solvents were removed *in vacuo*, co-evaporating with dioxane (2x5ml). The residue was taken up in DCM (7 ml) to which was added DIPEA (0.68mmol) and 1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrole-3-carbaldehyde (90 mg, 0.373mmol) and the mixture stirred for 10 minutes. MP-BH(OAc)₃ (500 mg, 3 eq) was then added and the reaction gently stirred for 3 hours. The reaction was filtered, washing with MeOH/DCM (1:1, 2 ml), and the filtrate reduced *in vacuo* to about 3 ml and then loaded onto a 40 g Biotage flash silica column and eluted with a gradient of EtOAc/MeOH/TEA

100:5:0.5 and heptane 10%-100% over 24x27 ml, to yield the product as a foam (186 mg, 55%).

¹H NMR (CDCl₃) δ 8.6 (bs, 1H), 7.9 (d, 1H), 7.6 (d, 1H), 7.4 (s, 1H), 7.35 (s, 1H), 7.25 (d, 1H), 7.1 (m, 4H), 6.9 (m, 4H), 6.2 (m, 2H), 3.4 (m, 2H), 2.3-2.7 (m, 7H), 2.0 (m, 1H),
5 1.45 (m, 1H).

¹³C NMR (CDCl₃): δ 171.2, 162.1 (2d, J=245), 153.3, 146.4 (q, J=4.2), 137.6 (2d, J=3.1), 136.0 (q, J=3.0), 129.2 (2d, J=7.6), 125.0, 123.8 (q, J=271), 122.8 (q, J=32), 118.5, 117.2, 115.6 (2d, J=21.5), 113.8, 110.5, 59.6, 55.7, 54.1, 52.3, 42.5, 33.8, 30.2.

MS (ESI+) 555.2 (M + 1H⁺); MS (ESI-) 553.1 (M - 1H⁺).

10

Example 12

***N*-(4-fluorophenyl)-1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide acetate**

- 15 a) **ethyl 1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxylate**

MP-BH(OAc)₃ (2.765 g, 5.72 mmol) was added to a stirred solution of ethyl piperidine-4-carboxylate (0.300 g, 1.91 mmol) and 1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrole-3-carbaldehyde (0.502 g, 2.10 mmol) in DCM (20 mL) and stirred overnight. The reaction
20 mixture was filtrated, concentrated and purified with Biotage Horizon Pioneer® HPFS using a silica cartridge with gradient elution n-Heptan / EtOAc:MeOH:TEA (100:5:0.5) to give the title compound in 0.648 g (89 %).

¹H NMR (CD₃OD) δ 8.62 (m, 1H), 8.05 (m, 1H), 7.52-7.62 (m, 3H), 6.32 (m, 1H), 4.09 (q, 2H), 3.40 (s, 2H), 2.89 (d, 2H), 2.27 (m, 1H), 2.06 (t, 2H), 1.82-1.89 (m, 2H), 1.64-1.76
25 (m, 2H), 1.20 (t, 3H).

- b) ***N*-(4-fluorophenyl)-1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide acetate**

Lithium hydroxide (0.102 g, 4.25 mmol) was dissolved in water (5 mL) and added to a
30 stirred solution of ethyl 1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxylate (0.648 g, 1.70 mmol) in tetrahydrofuran (10 mL), and stirred over night at room temperature. 4M HCl in 1,4-dioxane (10 mL) was added to the

reaction mixture, and the mixture was evaporated. Acetonitrile: Water (1:1, 10 mL) was added to the reaction mixture and freeze-dried.

(4-fluorophenyl)amine (0.017 g, 0.16 mmol), HATU (0.059 g, 0.16 mmol) and DIPEA (0.091 g, 0.71 mmol) were added to the freeze-dried product (0.14 mmol) dissolved in DMF (5 mL) and stirred for 18 hours at room temperature. The organic phase was purified by preparative HPLC to give the title compound in 0.053 g (74%).

¹H NMR (CD₃OD) δ 8.70 (m, 1H), 8.14 (d, 1H), 7.79 (s, 1H), 7.68-7.74 (m, 2H), 7.50-7.55 (m, 2H), 7.01 (t, 2H), 6.45 (m, 1H), 3.90 (s, 2H), 3.36 (m, 2H), 2.60-2.69 (m, 2H), 2.48-2.57 (m, 1H), 1.96-2.02 (m, 4H), 1.93 (s, 3H).

MS (ESI+) 446.8(M + 1H⁺), MS (ESI-) 444.9(M - 1H⁺).

Example 13

N-methyl-*N*-phenyl-*N'*-[1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea

1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-amine dihydrochloride (0.060 g, 0.138 mmol), methyl(phenyl)carbamic chloride (0.028 g, 0.165 mmol) and DIPEA (144 mL, 0.825 mmol) were dissolved in anhydrous THF (5 mL) and stirred at room temperature for 18 h. The organic phase was then concentrated *in vacuo* and purified with Biotage Horizon Pioneer® HPFS using a silica cartridge with a gradient elution of EtOAc/MeOH/TEA (100:3:0.3) in EtOAc to give the title compound as an oil 0.012 g (16 %).

¹H NMR (CDCl₃) δ 8.63 (s, 1H), δ 7.91 (d, 1H), δ 7.46 (t, 1H), δ 7.42 – 7.36 (m, 3H) δ 7.32 (d, 1H), δ 7.27 (t, 1H), δ 7.21 (dd, 2H), δ 6.30 (dd, 1H), δ 4.16 (d, 1H), δ 3.66 (m, 1H), δ 3.38 (s, 1H), δ 3.24 (s, 3H), δ 2.77 (d, 2H), δ 2.09 (t, 2H), δ 1.87 (d, 2H), δ 1.28 (q, 2H).

MS (ESI+) 458.2 (M + 1H⁺).

Example 14

N-(1,3-benzothiazol-2-ylmethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide

a) **Ethyl [1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl}piperidin-4-yl]acetate**

Ethyl piperidin-4-ylacetate (1.40 g, 8.18 mmol) dissolved in DCM (10 ml) was added to a solution of 1-[4-(trifluoromethyl)phenyl]-1H-pyrrole-3-carbaldehyde (2.35 g, 9.81 mmol) and sodium triacetoxymethylborohydride (5.20 g, 24.53 mmol) in DCM (20 ml). The reaction was allowed to stir at room temperature for 20 h and then quenched by the addition of water (20 ml). The organic phase was separated through a phase separator, concentrated *in vacuo* and purified with Biotage Horizon Pioneer® HPFS using a silica cartridge with a gradient elution of EtOAc/MeOH/TEA (100:10:1) in EtOAc to give the title compound as a solid 2.39 g (74 %).

¹H NMR (CDCl₃) δ 7.65 (d, 2H), δ 7.44 (d, 2H), 7.0 – 7.8 (m, 2 H), δ 6.30 (dd, 1H), δ 4.09 (q, 2H), δ 3.54 (s, 2H), δ 3.05 (d, 2H), δ 2.21 (d, 2H), δ 2.09 (t, 2H), δ 1.85 – 1.66 (m, 3H), δ 1.39 (dq, 2H), δ 1.22 (t, 2H).

b) **[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl}piperidin-4-yl]acetic acid - chlorolithium (1:2) hydrochloride**

Lithium hydroxide (0.29 g, 12.12 mmol) dissolved in water (7 ml) was added to a solution of ethyl [1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl}piperidin-4-yl]acetate (2.39 g, 6.06 mmol) in THF (25 ml). The mixture was stirred at room temperature for 16 h and the solvents evaporated *in vacuo*. The residue was dissolved in 4 M HCl in dioxane (25 ml) and stirred at room temperature for 1 h before it was freeze-dried, yielding 3.208 g of a solid. The reaction was assumed to have 100 % conversion.

¹H NMR (CD₃OD) δ 7.76 (d, 2H), δ 7.71 (d, 2H), δ 7.57 (s, 1H), δ 7.39 (t, 1H), δ 6.50 (dd, 1H), δ 4.21 (s, 2H), δ 3.55 (d, 2H), δ 2.98 (t, 2H), δ 2.28 (d, 2H), δ 2.01 (d, 3H), δ 1.54 (m, 2H).

MS (ESI+) 367.1 (M + 1H⁺), MS (ESI-) 365.1 (M - 1H⁺).

c) **N-(1,3-benzothiazol-2-ylmethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide**

4 ml of a stock solution containing [1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl}piperidin-4-yl]acetic acid - chlorolithium (1:2) hydrochloride (1.33 g, 2.73 mmol), DIPEA (1.41 g, 10.9 mmol) and HATU (1.24 g, 3.27 mmol) in DMF (100 ml) was

added to a reaction vial containing 1-(1,3-benzothiazol-2-yl)methanamine hydrochloride (0.026 g, 0.13 mmol). The reaction was allowed to stir at room temperature for 16 h and was then evaporated in a vacuum centrifuge at 40 °C for 5 h. The remaining oil was dissolved in DCM (3 ml) and shaken with 1 % NaHCO₃ (4 ml). The organic phase was separated through a phase separator and evaporated in a vacuum centrifuge at 20° C for 3 h. The remaining oil was purified by Automated Preparative HPLC to give the title product 0.030 g (54 %).

¹H NMR ((CD₃)₂SO) δ 8.84 (t, 1H), δ 8.05 (d, 1H), δ 7.92 (d, 1H), δ 7.79 (m, 4H), δ 7.52 – 7.37 (m, 4H), δ 6.28 (s, 1H), δ 4.65 (d, 2H), δ 3.50 – 3.35 (m, 2H), δ 2.94 (s, 2H), δ 2.13 (d, 2H), δ 2.15 – 1.89 (s, 2H), δ 1.82 – 1.64 (m, 1H), δ 1.69 (d, 2H), δ 1.32 – 1.16 (m, 2H). MS (ESI+) 513.1 (M + 1H⁺), MS (ESI-) 511.2 (M - 1H⁺).

Example 15-48

Using the method described for the preparation of the compound of Example 14, the compounds of Example 15-48 were prepared by reaction of [1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl}piperidin-4-yl]acetic acid - chlorolithium (1:2) hydrochloride with commercially available amines. The isolated yields of the products were in the range 17-75 % with purity in excess of 95% (assessed by HPLC-UV and ¹H NMR)

Example	Compound Name	MS (ESI+) (M+1H+)
15	N-(2-furylmethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide	446.1
16	N-(2-pyridin-2-ylethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide	471.1
17	N-(2,4-dichlorobenzyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide	524
18	N-(1,2-diphenylethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide	546.2

19	N-(1,3-benzodioxol-5-ylmethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	500.1
20	N-ethyl-N-(2-pyridin-2-ylethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	499.2
21	N-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	514.1
22	N-[3-(1H-imidazol-1-yl)propyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	474.1
23	N-(2,4-dichlorobenzyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	470.1
24	N-(4-fluorophenyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	460.1
25	N-[phenyl(pyridin-2-yl)methyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	533.2
26	N-[3-(difluoromethoxy)benzyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	522.1
27	1-(3-methoxyphenyl)-4-([1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetyl)piperazine	541.2
28	1'-([1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetyl)spiro[indene-1,4'-piperidine]	534.2
29	N-(3,3-diphenylpropyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	560.2
30	N-(1-phenylpropyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	484.1
31	N-(4-fluorophenyl)-N-methyl-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	474
32	N-[(1R,2S)-2-phenylcyclopropyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	482.1

33	N-(3-methylbutyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	436
34	N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methyl-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	544.2
35	N-[2-(3,4-dimethoxyphenyl)ethyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	530.2
36	N-[4-(1,2,3-thiadiazol-4-yl)benzyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	540.1
37	N-[1-(2,3-dihydro-1,4-benzodioxin-5-yl)ethyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	528.1
38	N,N-diethyl-1-{{1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl}acetyl}piperidine-3-carboxamide	533.3
39	N-1-adamantyl-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	500.2
40	N-[2-(4-methoxyphenoxy)ethyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	516.1
41	N-((1S)-1-[(benzyloxy)methyl]propyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	528.2
42	N-[(1R)-1-(3-methoxyphenyl)ethyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	500.1
43	N-{{3-(4-methoxyphenyl)isoxazol-5-yl}methyl}-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	553.1
44	4-(4-chlorophenyl)-1-{{1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl}acetyl}-1,2,3,6-tetrahydropyridine	542.1
45	N-[(1S,2S)-2-(benzyloxy)cyclopentyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	540.2
46	N-(1-methyl-1-phenylethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide	484.2

47	N-[(1-methyl-1H-pyrrol-2-yl)methyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide	459.1
48	4-(2-oxo-2-pyrrolidin-1-ylethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl}piperidine	420.1

Example 49***N*-(2-pyridin-2-ylethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide**

5

a) Ethyl 1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxylate

Ethyl piperidine-4-carboxylate (1.35 g, 8.59 mmol) dissolved in DCM (5 ml) was added to a solution of 1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrole-3-carbaldehyde (2.56 g, 10.69 mmol) and sodium triacetoxymethylborohydride (5.46 g, 25.8 mmol) in DCM (20 ml). The reaction was allowed to stir at room temperature for 6 h and was then quenched by addition of water (20 ml). The organic layer was separated through a phase separator, concentrated *in vacuo* and purified with Biotage Horizon Pioneer® HPFS using a silica cartridge with a gradient elution of EtOAc/MeOH/TEA (100:10:2) in EtOAc to give the title compound as a solid 2.64 g (81 %).

¹H NMR (CDCl₃) δ 7.65 (d, 2H), δ 7.44 (d, 2H), δ 7.08 – 7.02 (m, 2H), δ 6.31 (dd, 1H), δ 4.11 (q, 2H), δ 3.56 (m, 2H), δ 2.99 (d, 2H), δ 2.36 – 2.14 (m, 3H), 1.98 – 1.77 (m, 4H), δ 1.22 (t, 3H).

b) 1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxylic acid - chlorolithium (1:2) hydrochloride

Lithium hydroxide (0.33 g, 13.90 mmol) dissolved in water (7 ml) was added to a solution of ethyl 1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxylate (2.64 g, 6.95 mmol) in THF (20 ml). The mixture was allowed to stir at room temperature for 3 days and was then evaporated *in vacuo*. 4 M HCl in dioxane (25 ml) was added to the remaining oil, stirred at room temperature for 1 h, concentrated and freeze-dried, yielding the title compound as a solid 0.90 g (27 %).

^1H NMR (CD_3OD) δ 7.77 – 7.61 (m, 5H), δ 7.37 (s, 1H), δ 6.60 (s, 1H), δ 4.27 (s, 2H), δ 3.55 (d, 2H), δ 3.16 (t, 2H), δ 2.66 (m, 1H), δ 2.27 – 1.95 (m, 4H).

c) ***N*-(2-pyridin-2-ylethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide**

4 ml of a stock solution containing 1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxylic acid - chlorolithium (1:2) hydrochloride (0.90 g, 1.90 mmol), DIPEA (0.98 g, 7.60 mmol) and HATU (0.87 g, 2.28 mmol) in DMF (100 ml) was added to a reaction vial containing 2-pyridin-2-ylethanamine (0.011 g, 0.09 mmol). The reaction was allowed to stir at room temperature for 16 h and was then evaporated in a vacuumcentrifuge at 50 °C for 4.5 h. The remaining oil was dissolved in DCM (4 ml) and shaken with 1 % NaHCO_3 (aq) (4 ml). The organic layer was separated through a phase separator, evaporated in a vacuum centrifuge at 20 °C for 3 h and purified by Automated Preparative HPLC to give the title product, 0.019 g (55%).

^1H NMR ($(\text{CD}_3)_2\text{SO}$) δ 8.48 (d, 1H), δ 7.78 (m, 5H), 7.68 (dt, 1H), 7.45 (t, 1H), 7.38 (s, 1H), 7.23 – 7.17 (m, 2H), 6.24 (t, 1H), 3.37 (q, 3H), 3.32 (s, 2H), 2.80 – 2.91 (m, 4H), 2.01 (m, 1H), 1.85 (dt, 2H), 1.61 – 1.50 (m, 3H).

MS (ESI+) 457.0 ($\text{M} + 1\text{H}^+$), MS (ESI-) 515.1 ($\text{M} - 1\text{H}^+$).

20 **Example 50-67**

Using the method described for the preparation of the compound of Example 49, the compounds of Example 50-67 were prepared by reaction of 1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxylic acid - chlorolithium (1:2) hydrochloride with commercially available amines. The isolated yields were in the range 27 – 55 % with purity in excess of 94 – 100 % (assessed by HPLC-UV and ^1H NMR)

Example	Compound Name	MS (ESI+) ($\text{M} + 1\text{H}^+$)
50	<i>N</i> -(2,4-dichlorobenzyl)-1-({1-[4-(trifluoromethyl)phenyl]-1 <i>H</i> -pyrrol-3-yl)methyl}piperidine-4-carboxamide	511.4

51	N-(1,2-diphenylethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl)piperidine-4-carboxamide	532.1
52	N-(1,3-benzodioxol-5-ylmethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl)piperidine-4-carboxamide	486
53	N-[2-(3,4-dimethoxyphenyl)ethyl]-1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl)piperidine-4-carboxamide	516.1
54	N-[4-(1,2,3-thiadiazol-4-yl)benzyl]-1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl)piperidine-4-carboxamide	526
55	N-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl)piperidine-4-carboxamide	500
56	N-[1-(2,3-dihydro-1,4-benzodioxin-5-yl)ethyl]-1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl)piperidine-4-carboxamide	514.1
57	N-[phenyl(pyridin-2-yl)methyl]-1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl)piperidine-4-carboxamide	519.1
58	N-[3-(difluoromethoxy)benzyl]-1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl)piperidine-4-carboxamide	508
59	N-[2-(4-methoxyphenoxy)ethyl]-1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl)piperidine-4-carboxamide	502
60	N-({(1S)-1-[(benzyloxy)methyl]propyl}-1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl)piperidine-4-carboxamide	514.1
61	N-({[3-(4-methoxyphenyl)isoxazol-5-yl)methyl]-1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl)piperidine-4-carboxamide	539.1
62	1-(3-methoxyphenyl)-4-{[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl)piperidin-4-yl]carbonyl}piperazine	527.1
63	4-(4-chlorophenyl)-1-({[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl)piperidin-4-yl]carbonyl}-1,2,3,6-tetrahydropyridine	528.1
64	N-[(1S,2S)-2-(benzyloxy)cyclopentyl]-1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl)piperidine-4-carboxamide	526.1

65	N-(3,3-diphenylpropyl)-1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl)piperidine-4-carboxamide	546.1
66	N-(1-phenylpropyl)-1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl)piperidine-4-carboxamide	470.1
67	N-(1,3-benzothiazol-2-ylmethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl)piperidine-4-carboxamide	499

Example 68

N-[(5-chloro-6-methoxypyridin-3-yl)(4-fluorophenyl)methyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1H-pyrrol-3-yl)methyl)piperidin-4-yl]acetamide

5

a) 5-chloro-N,6-dimethoxy-N-methylnicotinamide

5-chloro-6-methoxynicotinic acid (0.900 g, 4.80 mmol) was dissolved in thionyl chloride (8 mL) and the solution was refluxed at 85 °C for 4 hours. The reaction was concentrated *in vacuo*, redissolved in DCM (6 mL) and *N,O*-dimethylhydroxylamine hydrochloride (0.562 g, 5.76 mmol) was added. The stirred mixture was cooled (0 °C) and TEA (2 mL) in DCM (2 mL) was added. The reaction mixture was allowed to warm to room temperature, was stirred for 18 h, was diluted with DCM (30 mL) and was washed with sat. NaHCO₃(aq.) / H₂O (9:1, 2x20 mL). The combined organic phase was dried over a phase separator and was evaporated *in vacuo* to give the title compound (1.0 g, 90 %).

¹H NMR (CDCl₃) δ 8.52 (s, 1H), 8.06 (s, 1H), 4.05 (s, 3H), 3.56 (s, 3H), 3.48 (s, 3H).

MS (ESI+) 231.1(M + 1H⁺).

b) (5-chloro-6-methoxypyridin-3-yl)(4-fluorophenyl)methanone

5-chloro-N,6-dimethoxy-N-methylnicotinamide (0.600 g, 2.60 mmol), dissolved in dry THF (4 mL), was added dropwise (30 min) to a stirred and cooled (-78 °C) solution of *n*-BuLi (1.6 M in hexane, 0.333 g) and 1-bromo-4-fluorobenzene (0.910 g, 5.20 mmol) in dry THF (10 mL). The reaction mixture was stirred at -78 °C for 2 hours followed by 1 hour at 0 °C. THF (10 mL) was added to the reaction mixture and the mixture was washed with 3M HCl (aq.) (10 mL). The water phase was extracted with diethyl ether. The THF solution was washed with sat. NaHCO₃ (aq.) / H₂O (9:1, 10 mL) and the combined organic

phases was dried with MgSO_4 , filtered and purified by preparative HPLC to give the title compound (0.230 g, 33%).

^1H NMR (CDCl_3) δ 8.38 (s, 1H), 8.04 (s, 1H), 7.76-7.72 (m, 2H), 7.13-7.09 (m, 2H), 4.025 (s, 3H).

c) (5-chloro-6-methoxypyridin-3-yl)(4-fluorophenyl)methanone oxime

(5-chloro-6-methoxypyridin-3-yl)(4-fluorophenyl)methanone (0.225 g, 0.847 mmol) and hydroxylamine hydrochloride (1.150 g, 16.55 mmol) was dissolved in EtOH (99.5%, 10 mL) and heated with microwave at 120 °C for 5 minutes. Concentrated *in vacuo* and to which was added sat. NaHCO_3 (aq.) / H_2O (9:1, 20 mL) and extracted with DCM, the combined organic phases were dried over MgSO_4 , filtered and concentrated *in vacuo* to give the title compound 0.244 g (103 %) as an oil.

^1H NMR (CDCl_3) (mixture of E and Z isomers) δ 9.80 (bs, 1H), 8.11 (s, $\frac{1}{2}\text{H}$), 7.99 (s, $\frac{1}{2}\text{H}$), 7.79 (s, 1H), 7.38 (m, 2H), 7.10 (m, 1H), 7.00 (m, 1H), 4.03 (s, $1\frac{1}{2}\text{H}$), 3.99 (m, $1\frac{1}{2}\text{H}$).

MS (ESI+) 281.1($\text{M} + 1\text{H}^+$), MS (ESI-) 278.9($\text{M} - 1\text{H}^+$).

d) [(5-chloro-6-methoxypyridin-3-yl)(4-fluorophenyl)methyl]amine

A mixture of (5-chloro-6-methoxypyridin-3-yl)(4-fluorophenyl)methanone oxime (0.244 g, 0.87 mmol) and ammonium acetate (0.114 g, 1.48 mmol) in ethanol (3 mL), water (2 mL) and NH_3 (26% aq, 2.5 mL) was heated to 80 °C. Zn powder (0.256 g, 3.91 mmol) was added portionwise to the reaction mixture over 1 hour. After 5 hours of stirring Zn powder (0.256 g, 3.91 mmol) and ammonium acetate (0.114 g, 1.48 mmol) were added to the reaction mixture and stirred for additional 18 hours at 80 °C. Sat. NaHCO_3 (aq.) / H_2O (1:1, 20 mL) was added to the reaction mixture and extracted with DCM, dried over MgSO_4 and concentrated *in vacuo* to give the title compound (0.187 g, 81 %).

^1H NMR (CDCl_3) δ 7.99 (s, 1H), 7.62 (s, 1H), 7.29 (m, 2H), 6.97 (m, 2H), 5.12 (s, 1H), 3.94 (s, 3H), 1.78 (bs, 2H).

e) tert-butyl 4-(2-[(5-chloro-6-methoxypyridin-3-yl)(4-fluorophenyl)methyl]amino)-2-oxoethyl)piperidine-1-carboxylate

[(5-chloro-6-methoxypyridin-3-yl)(4-fluorophenyl)methyl]amine (0.187 g, 0.701 mmol) was added dropwise to a stirred solution of [1-(*tert*-butoxycarbonyl)piperidin-4-yl]acetic acid (0.243 g, 0.84 mmol), EDC (0.161 g, 0.84 mmol) and HOAt (0.115 g, 0.84 mmol) in DCM (5 mL), and stirred for 5 hours at room temperature. Sat. NaHCO₃ (aq.) / H₂O (9:1, 30 mL) was added and extracted with DCM, dried over MgSO₄, filtered and concentrated *in vacuo* and purified with Biotage Horizon Pioneer® HPFC using a silica cartridge with elution EtOAc / n-Heptane (45:55) to give the title compound (0.307 g, 89%). MS (ESI+) 492.1(M + 1H⁺), MS (ESI-) 490.0(M - 1H⁺).

f) *N*-[(5-chloro-6-methoxypyridin-3-yl)(4-fluorophenyl)methyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide. *tert*-butyl 4-(2-[(5-chloro-6-methoxypyridin-3-yl)(4-fluorophenyl)methyl]amino)-2-oxoethylpiperidine-1-carboxylate (0.154 g, 0.31 mmol) was dissolved in 4M HCl (aq) in dioxane (10 mL) and stirred for 1 hour, concentrated *in vacuo* and redissolved in DCM (10 mL) and DIPEA (0.121 g, 0.94 mmol) followed by addition of 1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrole-3-carbaldehyde (0.090 g, 0.38 mmol) and MP-triacetoxyborohydride (0.544 g, 1.13 mmol of H⁻). The mixture was stirred over night at room temperature, filtered, concentrated *in vacuo* and purified on preparative HPLC to give the title compound 0.110 g (57%) as a solid.

¹H NMR (CDCl₃) δ 7.90 (s, 1H), 7.63 (d, 2H, *J*=8.5 Hz), 7.43 (m, 3H), 7.14 (m, 2H), 6.97-7.05 (m, 4H), 6.29 (s, 1H), 6.14 (d, 1H, *J*=8.47 Hz), 6.00 (d, 1H, *J*=8.47 Hz), 3.97 (s, 3H), 3.41 (s, 2H), 2.93 (d, 2H, *J*=10.6 Hz), 2.13 (d, 2H, *J*=7.2 Hz), 1.95 (t, 2H, *J*=10.6 Hz), 1.81 (m, 1H), 1.66 (m, 2H), 1.29 (m, 2H).

MS (ESI+) 615.2(M + 1H⁺)

Example 69

N-[(5-chloro-6-oxo-1,6-dihydropyridin-3-yl)(4-fluorophenyl)methyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide acetate salt

N-[(5-chloro-6-methoxypyridin-3-yl)(4-fluorophenyl)methyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide (0.100 g, 0.163 mmol, from Example 68) and pyridine hydrochloride (0.225 g, 1.95 mmol) was heated at 145 °C for 5 minutes. The reaction mixture was allowed to cool to room temperature, then

dissolved in H₂O / acetonitrile (1:1) and purified on prep-HPLC to give the title compound in 0.039 g (36%) as the acetate salt.

¹H NMR (CD₃OD) δ 7.75 (d, 2H, J=8.5 Hz), 7.68 (d, 2H, J=8.5 Hz), 7.60 (m, 1H), 7.44 (s, 1H), 7.34 (m, 1H), 7.28 (m, 2H), 7.15 (m, 1H), 7.09 (t, 2H, J=8.5 Hz), 6.44 (bs, 1H), 5.98 (s, 1H), 3.99 (s, 2H), 3.36 (d, 2H, J=11.4 Hz), 2.70 (t, 2H, J=12.5 Hz), 2.25 (d, 2H, J=7.2 Hz), 1.97 (m, 1H), 1.90 (s, 4H, AcOH), 1.84 (m, 2H), 1.54-1.42 (m, 2H).

MS (ESI+) 601.2(M + 1H⁺)

Example 70

10 ***N*-(4-chloro-2-methoxybenzyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide**

a) (4-chloro-2-methoxyphenyl)methanol

4-chloro-2-methoxybenzoic acid (2.00 g, 10.72 mmol) and TEA (1.94 ml, 13.9 mmol) were dissolved in THF (25 ml) and cooled to -20 °C. Isobutyl chloridocarbonate (1.90 g, 13.9 mmol) was added and the reaction was stirred for 2 h during which time a white precipitate was formed. The precipitate was filtered off, washed with THF and the flask was again cooled to -20 °C. Sodium borohydride (1.22 g, 32.2 mmol) was added along with a few drops of water resulting in vigorous gas evolution. The rest of the water (14 ml) was added when the gas evolution had decreased. The cooling bath was removed and the reaction was stirred for 16 h. Conc. HCl was added dropwise until the gas formation had ceased. THF was then evaporated *in vacuo*, the aqueous solution basified to pH 10 with NaHCO₃ (s), diluted with water and extracted twice with DCM. The combined organics were dried through a phase separator and concentrated *in vacuo*. Purification was done with Biotage Horizon Pioneer® HPFC using a silica cartridge with a gradient elution of 5 - 40 % EtOAc in heptane yielding the title compound as a solid 1.16 g (63 %).

¹H NMR (CDCl₃) δ 7.17 (d, 1H), 6.89 (d, 1H), 6.82 (s, 1H), 4.57 (s, 2H), 3.79 (s, 3H), 2.80 (s, OH).

30 **b) 4-chloro-1-(chloromethyl)-2-methoxybenzene**

(4-chloro-2-methoxyphenyl)methanol (1.16 g, 6.72 mmol) and TEA (1.87 ml, 13.4 mmol) were dissolved in DCM and in an icebath under an N₂ atmosphere. Methanesulfonyl

chloride (679 μ l, 8.74 mmol) was added over a period of 30 min and the reaction stirred at 0 °C for 2 h. DCM and 1 M HCl (aq.) were added, the phases separated and the aqueous phase extracted with DCM. The combined organics were dried through a phase separator and evaporated *in vacuo*. Purification was done with Biotage Horizon Pioneer® HPFS using a silica cartridge with a gradient elution of 0-30 % EtOAc in heptane yielding the title compound as a white solid 622 mg (48 %).

^1H NMR (CDCl_3) δ 7.25 (d, 1H), 6.91 (dd, 1H), 6.86 (d, 1H), 4.54 (s, 2H), 3.83 (s, 3H).

^{13}C NMR (CDCl_3) δ 158.1, 135.6, 131.5, 124.7, 120.9, 111.8, 56.0, 41.1.

10 **c) 1-(azidomethyl)-4-chloro-2-methoxybenzene**

4-chloro-1-(chloromethyl)-2-methoxybenzene (622 mg, 3.26 mmol) was dissolved in DMF and NaN_3 (423 mg, 6.51 mmol) was added followed by a few drops of water. The reaction was stirred at room temperature for 16 h. It was then poured on to water and extracted with ether (3x). The combined organic layers were washed with water dried through a phase separator and evaporated *in vacuo* and was used in the following step without further purification.

^1H NMR (CDCl_3) δ 7.15 (d, 1H), 6.92 (dd, 1H), 6.88 (ds, 1H), 4.29 (s, 2H), 3.83 (s, 3H).

d) 1-(4-chloro-2-methoxyphenyl)methanamine

20 1-(azidomethyl)-4-chloro-2-methoxybenzene (560 mg, 2.83 mmol) was dissolved in THF (10 ml) to which was added subsequently triphenylphosphine (1.04 g, 3.97 mmol) and water (143 μ l, 7.93 mmol) and the reaction was then stirred at rt for 3 days. The reaction mixture was then poured over 1 M HCl and separated with EtOAc. The organic phase was washed with 1 M HCl. The combined aqueous phases were basified to pH 10 with sat. Na_2CO_3 (aq) and extracted with DCM. The combined organic phases were dried through a phase separator and evaporated *in vacuo* to yield 443 mg (97 %) which was used in the next step without further purification.

^1H NMR (CDCl_3) δ 7.12 (d, 1H), 6.87 (dd, 1H), 6.82 (ds, 1H), 3.82 (s, 3H), 3.75 (s, 2H), 1.48 (s, 2H).

30

e) tert-butyl 4-[[[(4-chloro-2-methoxybenzyl)amino]carbonyl]piperidine-1-carboxylate

1-(*tert*-butoxycarbonyl)piperidine-4-carboxylic acid (220 mg, 0.961 mmol), HOAt (130 mg, 0.961 mmol) and EDC (181 mg, 0.961 mmol) were dissolved in DCM (8 ml) and stirred for 10 min before addition of 1-(4-chloro-2-methoxyphenyl)methanamine (150 mg, 0.874 mmol) dissolved in DCM (2 ml). The reaction was stirred at rt for 16 h and was then
5 separated between DCM and 0.1 M KHSO₄ (aq). The aqueous phase was extracted with DCM and the combined organic phases were washed twice with 5 % Na₂CO₃ (aq), dried through a phase separator and evaporated *in vacuo*. Purification was done with Biotage Horizon Pioneer® HPFC using a silica cartridge with a gradient elution of 5 - 50 % EtOAc/MeOH/TEA 100:3:0.3 in EtOAc yielding the title compound as a white solid 279
10 mg (83 %).

¹H NMR (CDCl₃) δ 7.08 (d, 1H), 6.82 (dd, 1H), 6.78 (ds, 1H), 6.12 (t, 1H), 4.30 (d, 2H), 4.05 (m, 2H), 3.78 (s, 3H), 2.65 (t, 2H), 2.17 (dt, 1H), 1.71 (dd, 2H), 1.55 (dq, 2H), 1.39 (s, 9H).

15 f) ***N*-(4-chloro-2-methoxybenzyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide**

tert-butyl 4-[[[(4-chloro-2-methoxybenzyl)amino]carbonyl]piperidine-1-carboxylate (279 mg, 0.727 mmol) was stirred with 4 M HCl in dioxane overnight. The solvent was coevaporated (3x) *in vacuo* with MeOH. The remaining salt was dissolved in DCM and
20 DIPEA (254 μl, 1.457 mmol). 1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrole-3-carbaldehyde (192 mg, 0.802 mmol) and NaBH(OAc)₃ (463 mg, 2.186 mmol) were added and the mixture was stirred at rt for 4 h. DCM and 5 % Na₂CO₃ (aq) were then added and the phases were separated. The aqueous phase was extracted twice with DCM, the combined organic phases dried through a phase separator and evaporated *in vacuo*. Purification was
25 done with Biotage Horizon Pioneer® HPFC using a silica cartridge with a gradient elution of 30 - 100 % EtOAc/MeOH/TEA 100:10:1 in EtOAc yielding the title compound as a white solid 283 mg (76 %).

¹H NMR (CDCl₃) δ 7.62 (d, 2H), 7.42 (d, 2H), 7.12 (d, 1H), 7.03 (t, 1H), 7.00 (t, 1H), 6.84 (dd, 1H), 6.80 (ds, 1H), 6.28 (dd, 1H), 5.97 (t, 1H), 4.34 (d, 2H), 3.80 (s, 3H), 3.40 (s, 2H),
30 δ 2.98 (dt, 2H), δ 2.06 (m, 1H), δ 1.94 (dt, 2H), 1.84 - 1.65 (m, 4H).

^{13}C NMR (CDCl_3) δ 174.9, 158.2, 143.2, 134.2, 130.6, δ 127.3 (q, $J=33.2$ Hz), δ 127.1 (q, $J=3.7$ Hz), δ 125.3, δ 124.3 (q, $J=271.6$ Hz), δ 123.7, 120.8, 119.6, 119.1, 118.3, 113.2, 111.3, 55.8, 55.6, 53.2, 43.7, 38.8, 29.2.

MS (ESI+) 506.2 ($\text{M} + 1\text{H}^+$)

Example 71

***N*-(4-chloro-2-hydroxybenzyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide, acetate salt**

N-(4-chloro-2-methoxybenzyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide (138 mg, 0.273 mmol, from Example 70) was dissolved in DCM (10 mL) and cooled in an ice bath under a N_2 atmosphere. Boron tribromide (1 M in DCM, 2.00 mmol) was slowly added and the reaction was then stirred for 2 h. The solvent was removed and 5 % NaHCO_3 (aq) (2 ml) was added. The solvent was evaporated *in vacuo*. Purification was done by preparative HPLC and yielded the title compound as a white solid 41 mg (27 %).

^1H NMR (CDCl_3) δ 7.82 (b, 1H), δ 7.64 (d, 2H), δ 7.42 (d, 2H), δ 7.08 (s, 1H), δ 7.05 (t, 1H), δ 7.02 – 6.94 (m, 2H), δ 6.83 (d, 1H), δ 6.71 (dd, 1H), δ 6.31 (m, 1H), δ 4.25 (d, 2H), δ 3.61 (s, 2H), δ 3.11 (dt, 2H), δ 2.31 – 2.17 (m, 3H), δ 2.00 (s, 3H), δ 1.94 – 1.80 (m, 4H). MS (ESI+) 492.2 ($\text{M} + 1\text{H}^+$)

Example 72

2-(3-fluorophenyl)-*N*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]pyrrolidine-1-carboxamide

a) **4-nitrophenyl [1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]carbamate**

5% aqueous Na_2CO_3 (130 mL) was added to a suspension of 1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-amine dihydrochloride (2.62 g, 6.61 mmol, from Example C) in DCM (130 mL). The mixture was stirred for 15 min and then the organic phase was separated through a phase separator. Bis(*p*-nitrophenyl)carbonate (2.01g, 6.61 mmol) was added and the resulting mixture stirred for 1h at room temperature. 5% aqueous Na_2CO_3 (130 mL) was added and the mixture stirred

for 15 min and then the organic phase was separated through a phase separator, diluted with DCM to a 154 mL stock solution.

b) **2-(3-fluorophenyl)-N-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]pyrrolidine-1-carboxamide**

1 mL of a 0.3M stock solution of DIPEA in DCM and 3.5 mL of a 0.043M stock solution of 4-nitrophenyl [1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]carbamate were added to 2-(3-fluorophenyl)pyrrolidine (50 mg, 0.30 mmol). The resulting mixture was stirred over night. 5% aqueous Na₂CO₃ (5 mL) was added and after 15 min the organic phase was separated through a phase separator and evaporated in a vacuum centrifuge. The remaining oil was purified by Automated Preparative HPLC to give the title compound 0.048 g (62 %).

¹H NMR ((CD₃)₂SO) δ 7.74 (s, 1H), 7.40 (t, 1H), 7.33-7.26 (m, 2H), 6.99-6.93 (m, 2H), 6.88 (d, 1H), 6.20-6.17 (m, 1H), 5.64 (d, 1H), 4.88 (dd, 1H), 3.54-3.47 (m, 1H), 3.41-3.25 (m, 4H obscured by H₂O-peak), 2.76-2.65 (m, 2H), 2.22-2.12 (m, 1H), 1.90-1.20 (m, 9H). MS (ESI+) 515.2 (M + 1H⁺).

Example 73-79

Using the method described for the preparation of the compound of Example 72, the compounds of Example 73-79 were prepared by reaction of 4-nitrophenyl [1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]carbamate with different amines. The isolated yields of the products were in the range 34-91% with purity in excess of 92% (assessed by HPLC-UV and ¹H NMR)

Example	Compound Name	MS (ESI+) (M+1H ⁺)
73	<i>N</i> -[2-(1 <i>H</i> -imidazol-1-yl)-1-phenylethyl]- <i>N'</i> -[1-({1-[4-(trifluoromethyl)phenyl]-1 <i>H</i> -pyrrol-3-yl}methyl)piperidin-4-yl]urea	537.3

74	<i>N</i> -(3-fluorobenzyl)- <i>N</i> -methyl- <i>N'</i> -[1-({1-[4-(trifluoromethyl)phenyl]-1 <i>H</i> -pyrrol-3-yl}methyl)piperidin-4-yl]urea	489.2
75	3-(1,1-dioxidothiomorpholin-4-yl)- <i>N</i> -[1-({1-[4-(trifluoromethyl)phenyl]-1 <i>H</i> -pyrrol-3-yl}methyl)piperidin-4-	540.2
76	<i>N</i> -(3-hydroxybutyl)- <i>N'</i> -[1-({1-[4-(trifluoromethyl)phenyl]-1 <i>H</i> -pyrrol-3-yl}methyl)piperidin-4-yl]urea	439.2
77	<i>N</i> -[(1 <i>S</i>)-2-hydroxy-1-phenylethyl]- <i>N'</i> -[1-({1-[4-(trifluoromethyl)phenyl]-1 <i>H</i> -pyrrol-3-yl}methyl)piperidin-4-yl]urea	487.2
78	2-(1,3-benzothiazol-2-yl)- <i>N</i> -[1-({1-[4-(trifluoromethyl)phenyl]-1 <i>H</i> -pyrrol-3-yl}methyl)piperidin-4-yl]pyrrolidine-1-carboxamide	554.2
79	2-(pyridin-3-ylmethyl)- <i>N</i> -[1-({1-[4-(trifluoromethyl)phenyl]-1 <i>H</i> -pyrrol-3-yl}methyl)piperidin-4-yl]pyrrolidine-1-carboxamide	512.3

Example 80

(+)-2-(3-fluorophenyl)-*N*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]pyrrolidine-1-carboxamide

5 2-(3-Fluorophenyl)-*N*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]pyrrolidine-1-carboxamide (305 mg, 0.593 mmol), the title compound of Example 72, was chromatographed on a Chiralpak AD 250x20 mm column, particle size 10µm, mobile phase MeOH/TFA 99.9/0.1, flow 15 mL/min, detection 254 nm at room temperature. The injected amount was 19 mg per run. The first peak was collected,
 10 evaporated and freeze dried from dioxane to give 126 mg (82 % of the theoretical yield), ee 99%.

MS (ESI) 515 ($M + 1H^+$).

Example 81

15 (-)-2-(3-fluorophenyl)-*N*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]pyrrolidine-1-carboxamide

See Example 80. The second peak was collected, evaporated and freeze dried from dioxane to give 136 mg (89 %), ee 99%.

MS (ESI) 515 ($M + 1H^+$).

Example 82

(+)-*N*-[2-(1*H*-imidazol-1-yl)-1-phenylethyl]-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea

5 *N*-[2-(1*H*-imidazol-1-yl)-1-phenylethyl]-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea (0.327 mg, 0.609 mmol), the title compound of Example 73, was chromatographed as described in Example 80. The injected amount was 35 mg per run. The first peak was collected, evaporated and freeze dried from dioxane to give 153 mg (94 %), ee >99%.

0 MS (ESI) 537 ($M + 1H^+$).

Example 83

(-)-*N*-[2-(1*H*-imidazol-1-yl)-1-phenylethyl]-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea

15 See Example 82. The second peak was collected, evaporated and freeze dried from dioxane to give 158 mg, ee >99%. The chemical purity was not satisfactory and the material was further purified on prep HPLC (Chromasil C8 50x300 mm) using CH₃CN/0.1M NH₄OAc 10/90 -> 100/0. The acetonitrile was evaporated and the aqueous phase was made alkaline with 2M NaOH and extracted with EtOAc three times. The combined organic layer was
20 washed with water, dried over Na₂SO₄ and evaporated. Yield: 114 mg (70 %) of pure product.

MS (ESI) 537 ($M + 1H^+$).

Example 84-87

25 Using the method described for the preparation of the compound of Example 72, the compounds of Example 84-87 were prepared by reaction of 4-nitrophenyl [1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]carbamate with different amines. The isolated yields of the products were in the range 23-34% with purity in excess of 97% (assessed by HPLC-UV and ¹H NMR).

Example	Compound Name	MS (ESI+) (M+1H ⁺)
84	2-(2-hydroxyethyl)- <i>N</i> -[1-({1-[4-(trifluoromethyl)phenyl]-1 <i>H</i> -pyrrol-3-yl}methyl)piperidin-4-yl]piperidine-1-carboxamide	479.2
85	<i>N</i> -(4-fluorobenzyl)- <i>N</i> -(3-hydroxypropyl)- <i>N'</i> -[1-({1-[4-(trifluoromethyl)phenyl]-1 <i>H</i> -pyrrol-3-yl}methyl)piperidin-4-yl]urea	533.2
86	<i>N</i> -(2-hydroxy-3-phenoxypropyl)- <i>N'</i> -[1-({1-[4-(trifluoromethyl)phenyl]-1 <i>H</i> -pyrrol-3-yl}methyl)piperidin-4-yl]urea	517.2
87	<i>N</i> -[(1-hydroxycyclohexyl)methyl]- <i>N'</i> -[1-({1-[4-(trifluoromethyl)phenyl]-1 <i>H</i> -pyrrol-3-yl}methyl)piperidin-4-yl]urea	479.2

Example 88

N-[(4-fluorophenyl)(6-methoxypyridin-3-yl)methyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide

a) *N*,6-dimethoxy-*N*-methylnicotinamide

Methyl 6-methoxynicotinate (1.500 g, 8.97 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (2.68 g, 26.02 mmol) were stirred in THF (20 mL) and cooled to -40 °C under argon. Isopropyl magnesium chloride (13 mL, 2M THF solution) was added during 15 minutes and the reaction mixture was stirred for 20 minutes. The reaction was quenched with 20% aq. AcOH, and the reaction mixture was extracted with diethyl ether. The water phase was basified with sat. aq. NaHCO₃ and extracted with DCM three times. The combined organic phases were dried over MgSO₄, filtered and concentrated *in vacuo* and purified by Biotage Horizon Pioneer® HPFC using a silica cartridge with gradient elution from 5 to 30% EtOAc in *n*-heptane to give the title compound (1.636 g, 93%).

MS (ESI+) 197.1(M + 1H⁺).

¹H NMR (CDCl₃) δ 8.64 (d, 1H, *J*=2.3 Hz), 7.98 (dd, 1H, *J*=2.5 Hz, *J*=8.8 Hz), 6.77 (d, 1H, *J*=8.8 Hz), 3.97 (s, 3H), 3.57 (s, 3H), 3.36 (s, 3H).

b) (4-fluorophenyl)(6-methoxypyridin-3-yl)methanone

N,6-dimethoxy-*N*-methylnicotinamide (0.500 g, 2.55 mmol) and 1-bromo-4-fluorobenzene (0.445 g, 2.55 mmol) were stirred in dry THF (15 mL) and cooled to -78 °C under argon. *n*-BuLi (0.326 g, 5.09 mmol, 1.6M THF solution) was added drop wise to the reaction mixture and after 20 minutes of stirring was 1M aq. HCl (10 mL) added followed by addition of EtOAc (40 mL). The organic phase was washed with water, brine and then dried over MgSO₄, filtered and concentrated *in vacuo* and purified with by Biotage Horizon Pioneer® HPFC using a silica cartridge with gradient elution from 0 to 15% EtOAc in *n*-heptane to give the title compound as an clear oil (0.225 g, 38%).

¹H NMR (CDCl₃) δ 8.56 (d, 1H, *J*=2.3 Hz), 8.04 (dd, 1H, *J*=2.7 Hz, *J*=8.9 Hz), 7.84 (m, 2H), 7.15 (m, 2H), 6.82 (d, 1H, *J*=8.9 Hz), 4.00 (s, 3H).

c) (*E*)-(4-fluorophenyl)(6-methoxypyridin-3-yl)methanone oxime

(4-fluorophenyl)(6-methoxypyridin-3-yl)methanone (0.225 g, 0.973 mmol), hydroxylamine hydrochloride (0.270 g, 3.89 mmol) and DIPEA (0.68 mL, 3.89 mmol) was dissolved in EtOH (99.5%, 5 mL) and heated in a microwave oven at 120 °C for 2x30 minutes. Additional hydroxylamine hydrochloride (0.250 g) was added and the reaction mixture was heated at 120 °C for 30 minutes. The reaction mixture was concentrated *in vacuo* and sat. NaHCO₃ (aq.) / H₂O (9:1, 20 mL) was added and the mixture was extracted with DCM. The combined organic phases were dried over MgSO₄, filtered and concentrated *in vacuo* to give the title compound (0.240 g, 100 %). MS (ESI+) 247.1(M + 1H⁺), MS (ESI-) 244.9(M - 1H⁺).

d) [(4-fluorophenyl)(6-methoxypyridin-3-yl)methyl]amine

A mixture of (*E*)-(4-fluorophenyl)(6-methoxypyridin-3-yl)methanone oxime (0.238 g, 0.97 mmol) and ammonium acetate (0.127 g, 1.64 mmol) in absolute ethanol (6 mL), water (4 mL) and NH₃ (26% aq, 5 mL) was heated to 80 °C. Zn powder (0.284 g, 4.35 mmol) was added portionwise to the reaction mixture over 1 hour and then stirred for 4 hour at 80 °C. Added sat. NaHCO₃ (aq.) / H₂O (1:1, 20 mL) to the reaction mixture and extracted with DCM three times. The combined organic phases was dried over a phase separator and concentrated *in vacuo* to give the title compound as a yellow oil (0.197 g, 88 %). MS (ESI+) 234.1(M + 1H⁺).

e) *tert*-butyl 4-(2-[[4-(4-fluorophenyl)(6-methoxypyridin-3-yl)methyl]amino]-2-oxoethyl)piperidine-1-carboxylate

The title compound was synthesised in 0.6 mmol scale using the same procedure as in Example 68, step e, by the use of HOBt instead of HOAt giving the title compound (0.238 g, 86%).

¹H NMR (CDCl₃) δ 8.02 (d, 1H, *J*=2.5 Hz), 7.36 (dd, 1H, *J*=2.6 Hz, *J*=8.9 Hz), 7.16-7.20 (m, 2H), 7.00-7.06 (m, 2H), 6.71 (d, 1H, *J*=8.3 Hz), 6.20 (d, 1H, *J*=8.3 Hz), 5.99 (d, 1H, *J*=7.9 Hz), 4.06 (bs, 2H), 3.92 (s, 3H), 2.96 (m, 2H), 2.16 (d, 2H, *J*=7.1 Hz), 2.00 (m, 1H), 1.60-1.74 (m, 2H), 1.45 (s, 9H), 1.06-1.18 (m, 2H).

f) *N*-[(4-fluorophenyl)(6-methoxypyridin-3-yl)methyl]-2-[1-([1-(4-(trifluoromethyl)phenyl)-1*H*-pyrrol-3-yl)methyl]piperidin-4-yl]acetamide

The title compound was synthesised in 0.520-mmol scale using the same procedure as in Example 68, step f, but purified with Biotage Horizon Pioneer® HPFC using a silica cartridge and elution by EtOAc:MeOH:TEA (100:5:0.5) to give the title compound as a clear oil (0.220 g, 73%).

¹H NMR (CDCl₃) δ 7.98 (d, 1H, *J*=2.6 Hz), 7.63 (d, 2H, *J*=8.5 Hz), 7.43 (d, 2H, *J*=8.5 Hz), 7.33 (dd, 1H, *J*=2.7 Hz, *J*=9.0 Hz), 7.11-7.18 (m, 2H), 6.94-7.06 (m, 3H), 6.65 (d, 1H, *J*=8.5 Hz), 6.53 (d, 1H, *J*=8.5 Hz), 6.30 (m, 1H), 6.15 (d, 1H, *J*=8.1 Hz), 3.87 (s, 3H), 3.40 (s, 2H), 2.92 (m, 2H), 2.76 (s, 1H), 2.11 (d, 2H, *J*=7.4 Hz), 1.81-1.98 (m, 2H), 1.74-1.84 (m, 1H), 1.60-1.68 (m, 2H), 1.21-1.34 (m, 2H).

MS (ESI+) 581.2(M + 1H⁺), MS (ESI-) 578.9(M - 1H⁺).

Example 89

N-[(4-fluorophenyl)(6-oxo-1,6-dihydropyridin-3-yl)methyl]-2-[1-([1-(4-(trifluoromethyl)phenyl)-1*H*-pyrrol-3-yl)methyl]piperidin-4-yl]acetamide

The title compound was synthesised in 0.344-mmol scale using the same procedure as in Example 69 giving the title compound as an 50% AcOH salt (0.153 g, 78%).

¹H NMR (CD₃OD) δ 7.76 (d, 2H, *J*=8.3 Hz), 7.69 (d, 2H, *J*=8.3 Hz), 7.43-7.48 (m, 2H), 7.35 (m, 1H), 7.27-7.32 (m, 2H), 7.19 (m, 1H), 7.07-7.12 (m, 2H), 6.52 (d, 1H, *J*=9.8 Hz),

6.44 (m, 1H), 6.01 (s, 1H), 3.95 (s, 2H), 3.29-3.37 (m, 2H), 2.64 (m, 2H), 2.27 (d, 2H, $J=7.2\text{Hz}$), 1.97 (m, 1H), 1.92 (s, 1.5H, AcOH), 1.79-1.88 (m, 2H), 1.43-1.55 (m, 2H).
MS (ESI+) 567.2(M + 1H⁺), MS (ESI-) 578.9(M - 1H⁺).

Example 90

N-[2-(2-methyl-1*H*-imidazol-1-yl)-1-phenylethyl]-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl)]urea

a) 2-(2-methyl-1*H*-imidazol-1-yl)-1-phenylethanone

2-methyl-1*H*-imidazole (1.07 g, 13.06 mmol) and K₂CO₃ (s) anhydrous (2.78 g, 20.09 mmol) was stirred in acetone (10 ml) for 5 min before addition of 2-bromo-1-phenylethanone (2.00 g, 10.05 mmol). The mixture was stirred at rt for 5 min during which time a milky solution and gas evolution were formed. The mixture was then heated at 140 °C for 15 min in a microwave. The solvent was evaporated. Separated between EtOAc (250 ml) and 5 % Na₂CO₃ (aq) (250 ml), the aqueous phase was washed with EtOAc (4x250 ml), the combined organics dried through a phase separator and evaporated *in vacuo*. Purification was done with Biotage Horizon Pioneer® HPFS using a silica cartridge with a gradient elution of 20 - 100 % EtOAc/MeOH/TEA 100:3:0.3 in EtOAc yielding the title compound as a white solid 1.11 g (48 %).
¹H NMR (CDCl₃) δ 7.92 (d, 2H), δ 7.61 (d, 1H), δ 7.48 (d, 2H), δ 6.91 (d, 1H), δ 6.75 (d, 1H), δ 5.25 (s, 2H), δ 2.22 (s, 3H).

b) 2-(2-methyl-1*H*-imidazol-1-yl)-1-phenylethanamine

2-(2-methyl-1*H*-imidazol-1-yl)-1-phenylethanone (400.0 mg, 2.00 mmol), NH₄OAc (3.08 g, 39.95 mmol) and Pol-BH₃CN (1.46 g, 5.99 mmol, 4.1 mmol/g) were dissolved in dry MeOH (10 ml). The reaction was heated in a microwave oven at 150 °C for 15 min. The resin was filtered off and washed with MeOH. The filtrate was collected and evaporated *in vacuo* and was then partitioned between DCM (150 ml) and 5 % Na₂CO₃ (aq) (150 ml). The aqueous phase was extracted with DCM (2x150 ml), the combined organic phases dried through a phase separator and evaporated *in vacuo* yielding the title compound as a colourless oil, 316 mg (79 %).

¹H NMR (CDCl₃) δ 7.34 – 7.20 (m, 5H), 6.85 (d, 1H), 6.78 (d, 1H), 4.23 (s, 1H), 3.92 (d, 2H), 2.13 (s, 3H), 2.20 – 1.70 (b, 2H).

c) ***N*-[2-(2-methyl-1*H*-imidazol-1-yl)-1-phenylethyl]-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]urea**

The title compound was prepared by reaction of 4-nitrophenyl [1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]carbamate with 2-(2-methyl-1*H*-imidazol-1-yl)-1-phenylethanamine according to the method described for the preparation of Example 72. Purification was done by preparative HPLC. Separated
between DCM (50 ml) and 5 % Na₂CO₃ (aq) (50 ml) and extracted the aqueous phase with DCM (2x50 ml). The combined organics were dried through a phase separator and evaporated *in vacuo* yielding the title compound as a white solid 80 mg (46 %).

¹H NMR (CDCl₃) δ 7.60 (d, 2H), 7.38 (d, 2H), 7.21 – 7.16 (m, 3 H), 7.02 – 6.95 (m, 4H), 6.63 (s, 1H), 6.38 (s, 1H), 6.26 – 6.20 (s, 2H), 5.95 (s, 1H), 5.03 (q, 1H), 4.12 (dd, 1H), 4.04 (dd, 1H), 3.68 – 3.48 (m, 1H), 3.36 (s, 2H), 2.82 (t, 2H), 2.01 (q, 2 H), 1.94 (s, 3H), 1.81 (dd, 2H), 1.32 (m, 2H).

¹³C NMR (CDCl₃) δ 157.8, 145.4, 143.1, 139.5, 129.0, 128.2, 127.4 (q, *J*=32.8 Hz), 127.1 (q, *J*=3.6 Hz), 126.8, 126.4, 124.2 (q, *J*=271.1 Hz), 123.3, 120.3, 119.7, 119.2, 118.5, 113.2, 55.3, 55.0, 52.4, 51.7, 47.2, 33.0, 12.7.

MS (ESI+) 551.3 (M + 1H⁺), MS (ESI-) 549.0 (M - 1H⁺).

Pharmacological Properties

MCH1 receptor radioligand binding.

Assays were performed on membranes prepared from CHO-K1 cells expressing the human Melanin concentrating hormone receptor 1 (hMCHR1, 5.45 pmol/mg protein; Euroscreen). Assays were performed in a 96-well plate format in a final reaction volume of 200 μl per well. Each well contained 6 μg of membrane proteins diluted in binding buffer (50 mM Tris, 3 mM MgCl₂, 0.05 % bovine serum albumin and the radioligand ¹²⁵I-MCH (IM344 Amersham) was added to give 10 000 cpm (counts per minute) per well. Each well contained 2 μl of the appropriate concentration of competitive antagonist prepared in DMSO and left to stand at 30 °C for 60 minutes. Non-specific binding was determined as

that remaining following incubation with 1 μ M MCH (Melanin concentrating hormone, H-1482 Bachem). The reaction was terminated by transfer of the reaction to GF/A filters using a Micro96 Harvester (Skatron Instruments, Norway). Filters were washed with assay buffer. Radioligand retained on the filters was quantified using a 1450 Microbeta TRILUX (Wallac, Finland).

Non-specific binding was subtracted from all values determined. Maximum binding was that determined in the absence of any competitor following subtraction of the value determined for non-specific binding. Binding of compounds at various concentrations was plotted according to the equation

$$y = A + \frac{(B - A)}{1 + ((C/x)^D)}$$

and IC_{50} estimated where

A is the bottom plateau of the curve i.e. the final minimum y value

B is the top of the plateau of the curve i.e. the final maximum y value

C is the x value at the middle of the curve. This represents the log EC_{50} value when $A + B = 100$

D is the slope factor. x is the original known x values. y is the original known y values.

The compounds exemplified herein had an IC_{50} of less than 1 μ M in the abovementioned human MCHr1 binding assay. Preferred compounds had an activity of less than 0.6 μ M.

For instance, the following IC_{50} values were obtained for the compounds of the following examples:

Example 2, 0.012 μ M

Example 3, 0.014 μ M

Example 6, 0.072 μ M

MCHr1 functional assay

Membranes expressing recombinant hMCHr1 (5.45 pmol/mg protein; Euroscreen) were prepared in assay buffer (50 mM HEPES, 100 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, 200 μ M DTT, 20 μ M GDP (Sigma) containing 0.1 μ g/ml BSA, pH7.4) before assay. The assays were performed using membranes at 6 μ g/well in an assay volume of 200 μ L and the appropriate concentrations of compounds prepared in DMSO. The reaction was started by addition of 0.056 nM [35 S]GTP γ S (Specific activity >1000 Ci/mmol; Amersham) and an

ED₈₀ concentration of MCH (determined for each membrane and each MCH batch). Non-specific binding was determined using 20 μ M non-radiolabelled GTP γ S. Plates were incubated for 45 min at 30°C. Free and bound GTP γ S were separated by filtration binding using GF/B filter mats presoaked in wash buffer (50 mM Tris, 5 mM MgCl₂, 50 mM NaCl, pH 7.4) using a Micro96 cell harvester (Skatron Instruments) and the filters then dried at 50°C before counting using a 1450 Microbeta TRILUX (Wallac).

Data are means \pm SD for experiments performed in triplicate. IC₅₀ values of antagonists were determined using non-linear regression analysis of concentration response curves using Activity Base. For instance, the following IC₅₀ values were obtained for the compounds of the following examples:

Example 1, 0.042 μ M

Example 2, 0.112 μ M

Diet induced obesity model in mouse

The utility of the compounds of the present invention in the treatment of obesity and related conditions is demonstrated by a decrease in body weight in cafeteria diet-induced obese mice. Female C57Bl/6J mice were given ad libitum access to calorie-dense 'cafeteria' diet (soft chocolate/cocoa-type pastry, chocolate, fatty cheese and nougat) and standard lab chow for 8-10 weeks until a body weight of 45-50 grams was achieved. Compounds to be tested were then administered systemically (iv, ip, sc or po) once daily for a minimum of 5 days, and the body weights of the mice monitored on a daily basis. During this period ad libitum access to calorie-dense 'cafeteria' diet and standard lab chow was maintained. Simultaneous assessment of adiposity was carried by means of DEXA imaging at baseline and termination of the study. Blood sampling was also carried out to assay changes in obesity-related plasma markers. Compounds of the invention gave a significant decrease in body weight, with the major effect being via a reduction in fat-mass.

hERG activity

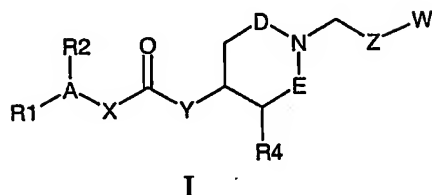
hERG testing was performed using a modified version of the method described by Kiss L, Bennett PB, Uebele VN, Koblan KS, Kane SA, Neagle B, Schroeder K. "High throughput ion-channel pharmacology: planar-array-based voltage clamp" *Assay Drug Dev Technol.* 1,

127-35. (2003). For example, the compounds of Examples 76 and 83 had IC₅₀ values exceeding 5 μ M in the abovementioned assay.

5 Compounds of the invention have the advantage that they may be more potent, more selective (e.g. vs. ion channels such as hERG and/or vs. GPCR's related to MCHr1) more efficacious in vivo, be less toxic, be longer acting, produce fewer side effects, be more easily absorbed, be less metabolised and/or have a better pharmacokinetic profile than, or have other useful pharmacological or physicochemical properties over, compounds known in the prior art.

Claims

1. A compound of formula I



A represents N, a C₁₋₄ alkyl group, a C₂₋₄ alkenyl group, C₃₋₈ cycloalkyl, adamantyl, azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, 1,3 oxazidinyl, tetrahydropyridinyl, or spiro[indene-1,4'-piperidinyl];

wherein said C₁₋₄ alkyl group or C₂₋₄ alkenyl group is optionally substituted by one or more fluoro;

X represents a bond or NR³,

wherein A and X do not both represent nitrogen;

wherein when A is azetidiny, 1,3 oxazidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyridinyl, or spiro[indene-1,4'-piperidinyl]; the nitrogen atom in A is directly attached to C(O),

R¹ and R² independently represent H, C₁₋₆ alkyl, a C₂₋₆ alkenyl group, C₃₋₁₀ cycloalkyl, CONR^aR^b in which R^a and R^b independently represent H, a C₁₋₄ alkyl group or R^a and R^b, together with the nitrogen to which they are attached, form a 4 to 8 membered heterocyclic ring;

phenyl or naphthyl; or

a heterocyclic group selected from pyrrolyl, imidazolyl, furyl, thienyl, thiazolyl, isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinolinyl, isoquinolyl, quinazolyl, indolyl, benzofuranyl, benzo[b]thienyl, benzimidazolyl, benzothiazolyl, 1,4-benzodioxinyl, 1,3-benzodioxolyl, piperidinyl, morpholinyl, 1,4-oxazepanyl, or 4,4-dioxothiomorpholinyl;

wherein R¹ or R² are optionally substituted by one or more of the following:

cyano

halo

hydroxy

oxo

a C₁₋₄ alkyl group optionally substituted by one or more fluoro;

a C₁₋₄ alkoxy group optionally substituted by one or more fluoro;

a group NCOR^aR^b or CONR^aR^b in which R^a and R^b independently represent a C₁₋₃ alkyl group;

a group SO₂C₁₋₄alkyl, optionally substituted by one or more fluoro;

an aryl or heteroaryl group selected from thiadiazolyl, pyrazolyl, phenyl, phenoxy, 2-pyridyl or 3-pyridyl wherein said aryl or heteroaryl group may optionally be further substituted by one or more of the following:

cyano,

halo,

hydroxy,

a C₁₋₄ alkyl group optionally substituted by one or more fluoro;

a C₁₋₄ alkoxy group optionally substituted by one or more fluoro;

a group NCOR^aR^b or CONR^aR^b in which R^a and R^b independently represent a C₁₋₃ alkyl group;

a group SO₂C₁₋₄alkyl, optionally substituted by one or more fluoro;

R¹ and/or R² is optionally linked to A via oxygen or via a C₁₋₄ alkyl group, wherein one of the carbon atoms in said C₁₋₄ alkyl group optionally is replaced with an oxygen atom,

Y represents NR³, C(R⁵:R⁶) or a bond,

wherein at least one of A, X or Y is N, NR³ or a nitrogen-containing heterocyclic ring,

R³, R⁵ and R⁶ independently represent H or a C₁₋₄ alkyl group,

D represents (CH₂)_n, wherein n is 0 or 1 and E represents (CH₂)_m, wherein m is 0 or 1,

R⁴ represents H or, when m and n are both 1, R₄ represents H or F,

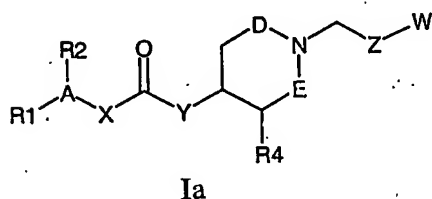
Z represents 2,5-thienyl, 2,5-furyl, or pyrrolyl, optionally substituted by one or more of the following: cyano, halo, a C₁₋₄ alkyl group optionally substituted by one or more fluoro, a C₁₋₄ alkoxy group optionally substituted by one or more fluoro,

W represents phenyl, 2-pyridyl or 3-pyridyl each of which is optionally substituted by one or more of the following: cyano, halo, a C₁₋₄ alkyl group optionally substituted by one or more fluoro, a C₁₋₄ alkoxy group optionally substituted by one or more fluoro, a trifluoromethylsulfonyl or a 2, 2'-difluoro-oxolanyl group (fused with two adjacent aromatic carbon atoms in W),

as well as tautomers, optical isomers and racemates thereof as well as pharmaceutically acceptable salts thereof,

with the proviso that when Y represents NR^3 then A-X does not represent OCH_2 , CH_2CH_2 or $\text{CH}=\text{CH}$, wherein each of the carbon atom may optionally be substituted by 1 to 2 methyl groups and/or 1 to 2 fluoro.

2. A compound of formula Ia



A represents N, a C_{1-4} alkyl group, a C_{2-4} alkenyl group, C_{3-8} cycloalkyl, adamantyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyridinyl, or spiro[indene-1,4'-piperidinyl];

wherein said C_{1-4} alkyl group or C_{2-4} alkenyl group is optionally substituted by one or more fluoro;

X represents a bond or NR^3 ,

wherein A and X do not both represent nitrogen;

wherein when A is pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydropyridinyl, or spiro[indene-1,4'-piperidinyl]; the nitrogen atom in A is directly attached to $\text{C}(\text{O})$,

R^1 and R^2 independently represent H, C_{1-6} alkyl, a C_{2-6} alkenyl group, C_{3-8} cycloalkyl,

CONR^aR^b in which R^a and R^b independently represent H, a C_{1-4} alkyl group or R^a and R^b , together with the nitrogen to which they are attached, form a 4 to 8 membered heterocyclic ring;

phenyl or naphthyl; or

a heterocyclic group selected from pyrrolyl, imidazolyl, furyl, thienyl, thiazolyl,

isothiazolyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, quinolinyl, isoquinolyl, quinazolyl, indolyl, benzofuranyl, benzo[b]thienyl,

benzimidazolyl, benzothiazolyl, 1,4-benzodioxinyl or 1,3-benzodioxolyl;

wherein R^1 or R^2 are optionally substituted by one or more of the following:

cyano

halo

hydroxy

a C₁₋₄ alkyl group optionally substituted by one or more fluoro;

a C₁₋₄ alkoxy group optionally substituted by one or more fluoro;

5 a group NCOR^aR^b or CONR^aR^b in which R^a and R^b independently represent a C₁₋₃ alkyl group;

a group SO₂C₁₋₄alkyl, optionally substituted by one or more fluoro;

an aryl or heteroaryl group selected from thiadiazolyl, pyrazolyl, phenyl, phenoxy, 2-pyridyl or 3-pyridyl wherein said aryl or heteroaryl group may optionally be further
10 substituted by one or more of the following:

cyano,

halo,

hydroxy,

a C₁₋₄ alkyl group optionally substituted by one or more fluoro;

15 a C₁₋₄ alkoxy group optionally substituted by one or more fluoro;

a group NCOR^aR^b or CONR^aR^b in which R^a and R^b independently represent a C₁₋₃ alkyl group;

a group SO₂C₁₋₄alkyl, optionally substituted by one or more fluoro;

R¹ and/or R² is optionally linked to A via oxygen or via a C₁₋₄ alkyl group, wherein one of
20 the carbon atoms in said C₁₋₄ alkyl group optionally is replaced with an oxygen atom,
Y represents NR³, C(R⁵·R⁶) or a bond,

wherein at least one of A, X or Y is N, NR³ or a nitrogen-containing heterocyclic ring,

R³, R⁵ and R⁶ independently represent H or a C₁₋₄ alkyl group,

D represents (CH₂)_n, wherein n is 0 or 1 and E represents (CH₂)_m, wherein m is 0 or 1,

25 R⁴ represents H or, when m and n are both 1, R₄ represents H or F,

Z represents 2,5-thienyl, 2,5-furyl, or pyrrolyl, optionally substituted by one or more of the
following: cyano, halo, a C₁₋₄ alkyl group optionally substituted by one or more fluoro, a
C₁₋₄ alkoxy group optionally substituted by one or more fluoro,

W represents phenyl, 2-pyridyl or 3-pyridyl each of which is optionally substituted by one
30 or more of the following: cyano, halo, a C₁₋₄ alkyl group optionally substituted by one or
more fluoro, a C₁₋₄ alkoxy group optionally substituted by one or more fluoro, a

trifluoromethylsulfonyl or a 2, 2'-difluoro-oxolanyl group (fused with two adjacent aromatic carbon atoms in W),

as well as tautomers, optical isomers and racemates thereof as well as pharmaceutically acceptable salts thereof,

5 with the proviso that when Y represents NR^3 then A-X does not represent OCH_2 , CH_2CH_2 or $\text{CH}=\text{CH}$, wherein each of the carbon atom may optionally be substituted by 1 to 2 methyl groups and/or 1 to 2 fluoro.

3. A compound according to claim 1 or 2, in which all compounds covered by claim 1 in
0 WO 01/14333 are excluded.

4. A compound according to any of the preceding claims, in which Y is CH_2 .

5. A compound according to any of the preceding claims, in which Z is 1,3-1H pyrrolyl (in
5 which the heteroatom is connected to W).

6. A compound according to any of the preceding claims, in which W is phenyl or 2- or 3-pyridyl substituted by trifluoromethyl.

20 7. A compound according to any of the preceding claims, in which A is NH, X is a bond and Y is CH_2 .

8. A compound according to any of the preceding claims, in which A is C_{1-4} alkyl, X is NH and Y is CH_2 .

25 9. A compound according to any of the preceding claims, in which A is NH, X is a bond and Y is a bond.

10. A compound according to any of the preceding claims, in which A is C_{1-4} alkyl, X is
30 NH and Y is a bond.

11. A compound according to any of the preceding claims, in which D represents $(CH_2)_n$, wherein n is 1 and E represents $(CH_2)_m$, wherein m is 1.
12. A compound according to any of the preceding claims, in which D represents $(CH_2)_n$, wherein n is 1 and E represents $(CH_2)_m$, wherein m is 0, or vice versa.
13. A compound according to any of the preceding claims, in which A represents pyrrolidinyl, piperidinyl, piperazinyl, or morpholinyl.
14. A compound according to any of the preceding claims, in which A. represents piperidinyl.
15. One or more of the following compounds:
- 2,2-diphenyl-*N*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- N*-(3,4-difluorobenzyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- N*-(2-phenylethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidine-4-carboxamide,
- N*-[bis(4-fluorophenyl)methyl]-2-[1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- N,N*-bis(4-fluorophenyl)-*N'*-[1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea,
- N*-[bis(4-fluorophenyl)methyl]-2-[1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl}methyl)pyrrolidin-3-yl]acetamide,
- N*-(4-fluorophenyl)-1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl}methyl)piperidine-4-carboxamide acetate,
- N*-(1,3-benzothiazol-2-ylmethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- N*-(2-furylmethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,

- N-(2-pyridin-2-ylethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- N-(2,4-dichlorobenzyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- 5 N-(1,2-diphenylethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide
- N-(1,3-benzodioxol-5-ylmethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- N-ethyl-N-(2-pyridin-2-ylethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- 10 N-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- N-[3-(1*H*-imidazol-1-yl)propyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- 15 N-(2,4-dichlorobenzyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- N-(4-fluorophenyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- N-[phenyl(pyridin-2-yl)methyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- 20 N-[3-(difluoromethoxy)benzyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- 1-(3-methoxyphenyl)-4-{[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetyl}piperazine,
- 25 1'-{[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetyl}spiro[indene-1,4'-piperidine],
- N-(3,3-diphenylpropyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide,
- N-(1-phenylpropyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide
- 30

- N-(4-fluorophenyl)-N-methyl-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide
- N-[(1*R*,2*S*)-2-phenylcyclopropyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide,
- 5 N-(3-methylbutyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide,
- N-[2-(3,4-dimethoxyphenyl)ethyl]-N-methyl-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide
- N-[2-(3,4-dimethoxyphenyl)ethyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide,
- 10 N-[4-(1,2,3-thiadiazol-4-yl)benzyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide,
- N-[1-(2,3-dihydro-1,4-benzodioxin-5-yl)ethyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide,
- 15 N,N-diethyl-1-([1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetyl)piperidine-3-carboxamide,
- N-1-adamantyl-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide,
- N-[2-(4-methoxyphenoxy)ethyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide
- 20 N-({1*S*)-1-[(benzyloxy)methyl]propyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide
- N-[(1*R*)-1-(3-methoxyphenyl)ethyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide
- 25 N-([3-(4-methoxyphenyl)isoxazol-5-yl]methyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide
- 4-(4-chlorophenyl)-1-([1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetyl)-1,2,3,6-tetrahydropyridine
- N-[(1*S*,2*S*)-2-(benzyloxy)cyclopentyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide
- 30

N-(1-methyl-1-phenylethyl)-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide

N-[(1-methyl-1*H*-pyrrol-2-yl)methyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidin-4-yl]acetamide

5 4-(2-oxo-2-pyrrolidin-1-ylethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine,

N-(2-pyridin-2-ylethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide,

10 N-(2,4-dichlorobenzyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide,

N-(1,2-diphenylethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide,

N-(1,3-benzodioxol-5-ylmethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide,

15 N-[2-(3,4-dimethoxyphenyl)ethyl]-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide,

N-[4-(1,2,3-thiadiazol-4-yl)benzyl]-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide,

20 N-(2,3-dihydro-1,4-benzodioxin-2-ylmethyl)-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide,

N-[1-(2,3-dihydro-1,4-benzodioxin-5-yl)ethyl]-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide,

N-[phenyl(pyridin-2-yl)methyl]-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide,

25 N-[3-(difluoromethoxy)benzyl]-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide,

N-[2-(4-methoxyphenoxy)ethyl]-1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl}piperidine-4-carboxamide,

- N-((1*S*)-1-((benzyloxy)methyl)propyl)-1-((1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl)piperidine-4-carboxamide,
- N-((3-(4-methoxyphenyl)isoxazol-5-yl)methyl)-1-((1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl)piperidine-4-carboxamide,
- 5 1-(3-methoxyphenyl)-4-((1-((1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl)piperidin-4-yl]carbonyl)piperazine,
- 4-(4-chlorophenyl)-1-((1-((1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl)piperidin-4-yl]carbonyl)-1,2,3,6-tetrahydropyridine,
- N-((1*S*,2*S*)-2-(benzyloxy)cyclopentyl)-1-((1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl)piperidine-4-carboxamide,
- 10 N-(3,3-diphenylpropyl)-1-((1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl)piperidine-4-carboxamide,
- N-(1-phenylpropyl)-1-((1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl)piperidine-4-carboxamide,
- 15 N-(1,3-benzothiazol-2-ylmethyl)-1-((1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl)piperidine-4-carboxamide,
- N-((5-chloro-6-methoxypyridin-3-yl)(4-fluorophenyl)methyl)-2-((1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl)piperidin-4-yl]acetamide,
- N-((5-chloro-6-oxo-1,6-dihydropyridin-3-yl)(4-fluorophenyl)methyl)-2-((1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl)piperidin-4-yl]acetamide acetate salt,
- 20 N-(4-chloro-2-methoxybenzyl)-1-((1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl)piperidine-4-carboxamide,
- N-(4-chloro-2-hydroxybenzyl)-1-((1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl)piperidine-4-carboxamide, acetate salt,
- 25 2-(3-fluorophenyl)-N-[1-((1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl)piperidin-4-yl]pyrrolidine-1-carboxamide,
- N-[2-(1*H*-imidazol-1-yl)-1-phenylethyl]-N'-[1-((1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl)methyl)piperidin-4-yl]urea,

- N*-(3-fluorobenzyl)-*N*-methyl-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea,
- 3-(1,1-dioxidothiomorpholin-4-yl)-*N*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]azetidine-1-carboxamide,
- 5 *N*-(3-hydroxybutyl)-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea,
- N*-[(1*S*)-2-hydroxy-1-phenylethyl]-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea,
- 2-(1,3-benzothiazol-2-yl)-*N*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]pyrrolidine-1-carboxamide,
- 10 2-(pyridin-3-ylmethyl)-*N*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]pyrrolidine-1-carboxamide,
- (+)-2-(3-fluorophenyl)-*N*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]pyrrolidine-1-carboxamide,
- 15 (-)-2-(3-fluorophenyl)-*N*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]pyrrolidine-1-carboxamide,
- (+)-*N*-[2-(1*H*-imidazol-1-yl)-1-phenylethyl]-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea,
- (-)-*N*-[2-(1*H*-imidazol-1-yl)-1-phenylethyl]-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea,
- 20 2-(2-hydroxyethyl)-*N*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]piperidine-1-carboxamide;
- N*-(4-fluorobenzyl)-*N*-(3-hydroxypropyl)-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea;
- 25 *N*-(2-hydroxy-3-phenoxypropyl)-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea;
- N*-[(1-hydroxycyclohexyl)methyl]-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea;

N-[(4-fluorophenyl)(6-methoxypyridin-3-yl)methyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide;

N-[(4-fluorophenyl)(6-oxo-1,6-dihydropyridin-3-yl)methyl]-2-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]acetamide; and

5 *N*-[2-(2-methyl-1*H*-imidazol-1-yl)-1-phenylethyl]-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea;

and pharmaceutically acceptable salts thereof.

16. *N*-[4-(trifluoromethoxy)phenyl]-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea and pharmaceutically acceptable salts thereof.

17. *N*-(2,4-dichlorophenyl)-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea and pharmaceutically acceptable salts thereof.

18. *N*-1-naphthyl-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea and pharmaceutically acceptable salts thereof.

19. *N*-(3-fluorobenzyl)-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea, and pharmaceutically acceptable salts thereof.

20. *N*-(diphenylmethyl)-*N'*-[1-({1-[4-(trifluoromethyl)phenyl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea, and pharmaceutically acceptable salts thereof.

21. *N*-methyl-*N*-phenyl-*N'*-[1-({1-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-pyrrol-3-yl}methyl)piperidin-4-yl]urea and pharmaceutically acceptable salts thereof.

22. A compound according to any of the claims 1 to 4, in which A is C₁ alkyl, X is NH and Y is NH.

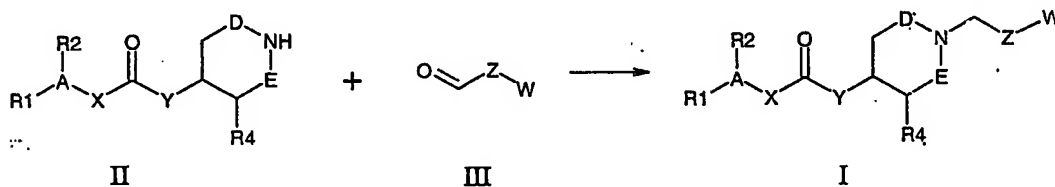
23. A compound of formula I or Ia as claimed in any one of claims 1 to 22 for use as a medicament.

24. A pharmaceutical formulation comprising a compound of formula I or Ia, as defined in any one of claims 1 to 22 and a pharmaceutically acceptable adjuvant, diluent or carrier.

25. Use of a compound of formula I or Ia as defined in any one of claims 1 to 22 in the preparation of a medicament for the treatment or prophylaxis of conditions associated with obesity.

26. A compound as defined in any one of claims 1 to 22 for use in the treatment of obesity.

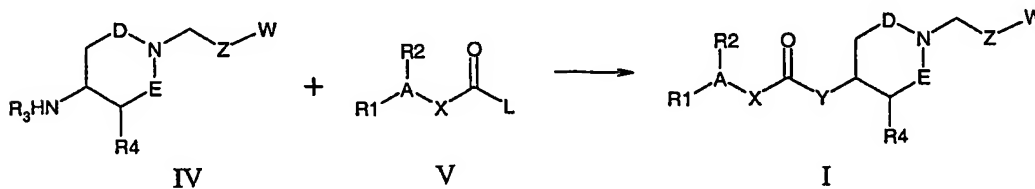
27. A process for the preparation of compounds of claim 3 comprising reacting a compound of formula II with a compound of formula III



in which A, X, Y, D, E, Z, W, R¹, R² and R⁴ are as previously defined.

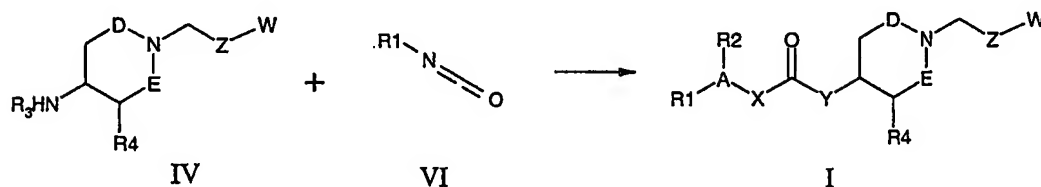
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28. A process for the preparation of compounds of claim 3 comprising reacting a compound of formula IV with a compound of formula V



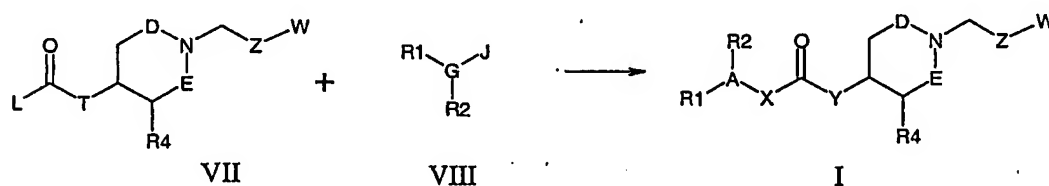
25 in which A, X, L, Y, D, E, Z, W, R¹, R² and R⁴ are as previously defined.

29. A process for the preparation of compounds of claim 3 comprising reacting a compound of formula VI with a compound of formula IV



5 in which A, X, Y, D, E, Z, W, R^1 , R^2 and R^4 are as previously defined.

30. A process for the preparation of compounds of claim 3 comprising reacting a compound of formula VI with a compound of formula IV



10 in which A, X, Y, D, E, Z, W, R^1 , R^2 , R^4 , L, T, G and J are as previously defined.

31. A method of treating obesity, psychiatric disorders, anxiety, anxio-depressive disorders, depression, bipolar disorder, ADHD, cognitive disorders, memory disorders, schizophrenia, epilepsy, and related conditions, and neurological disorders and pain related disorders, comprising administering a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 22 to a patient in need thereof.

32. A method of treating obesity, type II diabetes, metabolic syndrome and prevention of type II diabetes comprising administering a pharmacologically effective amount of a compound as claimed in any one of claims 1 to 22 to a patient in need thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2005/001966

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 31-32
because they relate to subject matter not required to be searched by this Authority, namely:

See extra sheet.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2005/001966

Continuation of Box No. II.1.:

Claims 31-32 relate to a method of treatment of the human or animal body (Rule 39.1(iv)). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2005/001966

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1604981 A1 (ONO PHARMACEUTICAL CO., LTD.), 14 December 2005 (14.12.2005), example 28(17), page 101; paragraphs (0110) och (0743) --	1-3,5-6,11, 23-24,31
X	WO 0114333 A1 (ASTRAZENECA UK LIMITED), 1 March 2001 (01.03.2001), page 22, line 1, examples 95,97,99 and 10; the claims --	1-2,5-6, 9-11,13-14, 22-24,31
A	WO 03106452 A2 (MILLENNIUM PHARMACEUTICALS, INC.), 24 December 2003 (24.12.2003) --	1-32
A	WO 2004081005 A1 (NEUROCRINE BIOSCIENCES, INC.), 23 Sept 2004 (23.09.2004) --	1-32

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

20 March 2006

Date of mailing of the international search report

21-03-2006

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE2005/001966

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03031410 A1 (NEUROCRINE BIOSCIENCES, INC.), 17 April 2003 (17.04.2003) --	1-32
A	WO 03028641 A2 (TAISHO PHARMACEUTICAL CO., LTD.), 10 April 2003 (10.04.2003) --	1-32
A	WO 2004087669 A1 (TAISHO PHARMACEUTICAL CO. LTD.), 14 October 2004 (14.10.2004) -- -----	1-32

International patent classification (IPC)

C07D 401/06 (2006.01)
A61K 31/4025 (2006.01)
A61K 31/4427 (2006.01)
A61K 31/4523 (2006.01)
A61K 31/496 (2006.01)
A61P 25/00 (2006.01)
A61P 3/04 (2006.01)
A61P 3/10 (2006.01)
C07D 401/14 (2006.01)
C07D 405/14 (2006.01)
C07D 413/14 (2006.01)
C07D 417/14 (2006.01)

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Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT
Information on patent family members

31/12/2005

International application No.
PCT/SE2005/001966

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				US	20040030754 A	12/02/2004
				US	20050197350 A	08/09/2005

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International Bureau



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4 May 2006 (04.05.2006)

PCT

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(25) Filing Language: English

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(30) Priority Data:
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(74) Common Representative: MERCK & CO., INC.; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

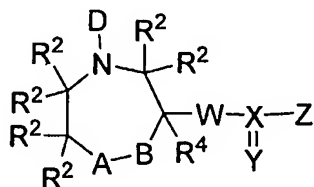
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

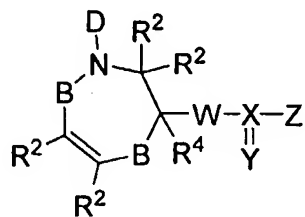
— without international search report and to be republished upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: CGRP RECEPTOR ANTAGONISTS



(I)



(II)

(57) Abstract: Compounds of Formula I and formula II (where variables D, R², R⁴, A, B, W, X, Y and Z are as defined herein) useful as antagonists of CGRP receptors and useful in the treatment or prevention of diseases in which the CGRP is involved, such as headache, migraine and cluster headache. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which CGRP is involved.

TITLE OF THE INVENTION

CGRP RECEPTOR ANTAGONISTS

BACKGROUND OF THE INVENTION

- 5 CGRP (Calcitonin Gene-Related Peptide) is a naturally occurring 37-amino acid peptide that is generated by tissue-specific alternate processing of calcitonin messenger RNA and is widely distributed in the central and peripheral nervous system. CGRP is localized predominantly in sensory afferent and central neurons and mediates several biological actions, including vasodilation. CGRP is expressed in alpha- and beta-forms that vary by one and three amino acids in the rat and human, respectively. CGRP-alpha and CGRP-beta display similar biological properties. When released from the cell, CGRP initiates its biological responses by binding to specific cell surface receptors that are predominantly coupled to the activation of adenylyl cyclase. CGRP receptors have been identified and pharmacologically evaluated in several tissues and cells, including those of brain, cardiovascular, endothelial, and smooth muscle origin.
- 10 Based on pharmacological properties, these receptors are divided into at least two subtypes, denoted CGRP₁ and CGRP₂. Human α -CGRP-(8-37), a fragment of CGRP that lacks seven N-terminal amino acid residues, is a selective antagonist of CGRP₁, whereas the linear analogue of CGRP, diacetoamido methyl cysteine CGRP ([Cys(ACM)₂,7]CGRP), is a selective agonist of CGRP₂. CGRP is a potent vasodilator that has been implicated in the pathology of cerebrovascular disorders such as migraine and cluster headache. In clinical studies, elevated levels of CGRP in the jugular vein were found to occur during migraine attacks (Goadsby et al., *Ann. Neurol.*, 1990, 28, 183-187). CGRP activates receptors on the smooth muscle of intracranial vessels, leading to increased vasodilation, which is thought to be the major source of headache pain during migraine attacks (Lance, *Headache Pathogenesis: Monoamines, Neuropeptides, Purines and Nitric Oxide*, Lippincott-Raven Publishers, 1997, 3-9). The middle meningeal artery, the principle artery in the dura mater, is innervated by sensory fibers from the trigeminal ganglion which contain several neuropeptides, including CGRP. Trigeminal ganglion stimulation in the cat resulted in increased levels of CGRP, and in humans, activation of the trigeminal system caused facial flushing and increased levels of CGRP in the external jugular vein (Goadsby et al., *Ann. Neurol.*, 1988, 23, 193-196). Electrical stimulation of the dura mater in rats increased the diameter of the middle meningeal artery, an effect that was blocked by prior administration of CGRP(8-37), a peptide CGRP antagonist (Williamson et al., *Cephalalgia*, 1997, 17, 525-531). Trigeminal ganglion stimulation increased facial blood flow in the rat, which was inhibited by CGRP(8-37) (Escott et al., *Brain Res.* 1995, 669, 93-99). Electrical stimulation of the trigeminal ganglion in marmoset produced an increase in facial blood flow that could be blocked by the non-peptide CGRP antagonist BIBN4096BS.

(Doods et al., Br. J. Pharmacol., 2000, 129, 420-423). Thus the vascular effects of CGRP may be attenuated, prevented or reversed by a CGRP antagonist.

CGRP-mediated vasodilation of rat middle meningeal artery was shown to sensitize neurons of the trigeminal nucleus caudalis (Williamson et al., The CGRP Family: Calcitonin Gene-Related Peptide (CGRP), Amylin, and Adrenomedullin, Landes Bioscience, 2000, 245-247). Similarly, distention of dural blood vessels during migraine headache may sensitize trigeminal neurons. Some of the associated symptoms of migraine, including extra-cranial pain and facial allodynia, may be the result of sensitized trigeminal neurons (Burstein et al., Ann. Neurol. 2000, 47, 614-624). A CGRP antagonist may be beneficial in attenuating, preventing or reversing the effects of neuronal sensitization.

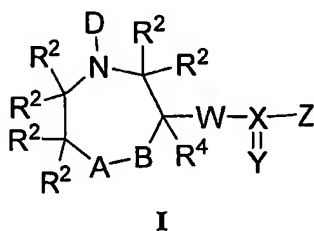
The ability of the compounds of the present invention to act as CGRP antagonists makes them useful pharmacological agents for disorders that involve CGRP in humans and animals, but particularly in humans. Such disorders include migraine and cluster headache (Doods, Curr Opin Inves Drugs, 2001, 2 (9), 1261-1268; Edvinsson et al., Cephalalgia, 1994, 14, 320-327); chronic tension type headache (Ashina et al., Neurology, 2000, 14, 1335-1340); pain (Yu et al., Eur. J. Pharm., 1998, 347, 275-282); chronic pain (Hulsebosch et al., Pain, 2000, 86, 163-175); neurogenic inflammation and inflammatory pain (Holzer, Neurosci., 1988, 24, 739-768; Delay-Goyet et al., Acta Physiol. Scand., 1992, 146, 537-538; Salmon et al., Nature Neurosci., 2001, 4(4), 357-358); eye pain (May et al., Cephalalgia, 2002, 22, 195-196), tooth pain (Awawdeh et al., Int. Endocrin. J., 2002, 35, 30-36), non-insulin dependent diabetes mellitus (Molina et al., Diabetes, 1990, 39, 260-265); vascular disorders; inflammation (Zhang et al., Pain, 2001, 89, 265), arthritis, bronchial hyperreactivity, asthma (Foster et al., Ann. NY Acad. Sci., 1992, 657, 397-404; Schini et al., Am. J. Physiol., 1994, 267, H2483-H2490; Zheng et al., J. Virol., 1993, 67, 5786-5791); shock, sepsis (Beer et al., Crit. Care Med., 2002, 30 (8), 1794-1798); opiate withdrawal syndrome (Salmon et al., Nature Neurosci., 2001, 4(4), 357-358) morphine tolerance (Menard et al., J. Neurosci., 1996, 16 (7), 2342-2351); hot flashes in men and women (Chen et al., Lancet, 1993, 342, 49; Spetz et al., J. Urology, 2001, 166, 1720-1723); allergic dermatitis (Wallengren, Contact Dermatitis, 2000, 43 (3), 137-143); psoriasis; encephalitis, brain trauma, ischaemia, stroke, epilepsy, and neurodegenerative diseases (Rohrenbeck et al., Neurobiol. of Disease 1999, 6, 15-34); skin diseases (Geppetti and Holzer, Eds., Neurogenic Inflammation, 1996, CRC Press, Boca Raton, FL), neurogenic cutaneous redness, skin rosaceousness and erythema; tinnitus (Herzog et al., J. Membrane Biology, 2002, 189(3), 225); inflammatory bowel disease, irritable bowel syndrome, (Hoffman et al. Scandinavian Journal of Gastroenterology, 2002, 37(4) 414-422) and cystitis. Of particular importance is the acute or prophylactic treatment of headache, including migraine and cluster headache. Compelling evidence of the efficacy of CGRP antagonists for the treatment of migraine has been provided by clinical studies using intravenously administered BIBN4096BS. This CGRP antagonist

was found to be a safe and effective acute treatment for migraine (Olesen et al., N. Engl. J. Med., 2004, 350(11), 1104-1110).

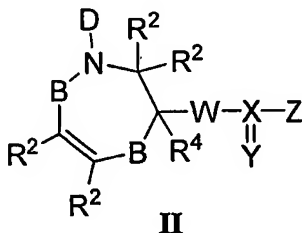
The present invention relates to compounds that are useful as ligands for CGRP receptors, in particular antagonists for CGRP receptors, processes for their preparation, their use in therapy, pharmaceutical compositions comprising them and methods of therapy using them.

SUMMARY OF THE INVENTION

The present invention is directed to compounds of Formula I:



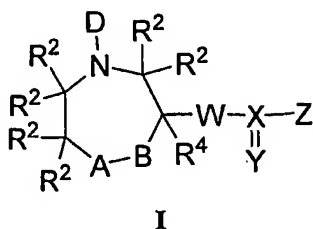
and Formula II:



(where variables D, R¹, R⁴, A, B, W, X, Y and Z are as defined herein) useful as antagonists of CGRP receptors and useful in the treatment or prevention of diseases in which the CGRP is involved, such as headache, migraine and cluster headache. The invention is also directed to pharmaceutical compositions comprising these compounds and the use of these compounds and compositions in the prevention or treatment of such diseases in which CGRP is involved.

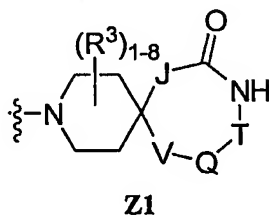
DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to CGRP antagonists which include compounds of Formula I:

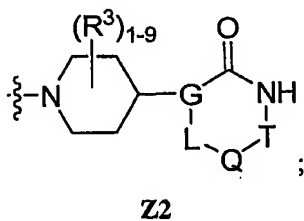


wherein:

Z is selected from:



and



A is a bond, C(R²)₂, O, S(O)_m or NR²;

20 B is (C(R²)₂)_n;

D is selected from R¹, OR¹, N(R¹)₂, NR¹C(O)R¹, C(O)R¹, S(O)_mR¹, C(O)OR¹, C(O)N(R¹)₂, C(O)NR¹⁰R¹¹, C(NR¹)N(R¹)₂ and C(NR¹)R¹;

25 R¹ is independently selected from:

- 1) H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-6 cycloalkyl, and heterocycle, unsubstituted or substituted with one or more substituents each independently selected from:
- a) C₁-6 alkyl,
 - b) C₃-6 cycloalkyl,
 - c) aryl, unsubstituted or substituted with 1-5 substituents each independently selected from R⁴,
 - d) heteroaryl, unsubstituted or substituted with 1-5 substituents each independently selected from R⁴,
 - e) heterocycle, unsubstituted or substituted with 1-5 substituents each independently selected from R⁴,
 - f) (F)_pC₁₋₃ alkyl,
 - g) halogen,
 - h) OR⁴,
 - i) O(CH₂)_s OR⁴,
 - j) CO₂R⁴,
 - k) (CO)NR¹⁰R¹¹,
 - l) O(CO)NR¹⁰R¹¹,
 - m) N(R⁴)(CO)NR¹⁰R¹¹,
 - n) N(R¹⁰)(CO)R¹¹,
 - o) N(R¹⁰)(CO)OR¹¹,
 - p) SO₂NR¹⁰R¹¹,
 - q) N(R¹⁰)SO₂R¹¹,
 - r) S(O)_mR¹⁰,
 - s) CN,
 - t) NR¹⁰R¹¹,
 - u) N(R¹⁰)(CO)NR⁴R¹¹, and
 - v) O(CO)R⁴, and
- 2) aryl or heteroaryl, unsubstituted or substituted with one or more substituents each independently selected from:
- a) C₁-6 alkyl,
 - b) C₃-6 cycloalkyl,

- c) aryl, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
- d) heteroaryl, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
- 5 e) heterocycle, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
- f) $(F)_p C_{1-3}$ alkyl,
- g) halogen,
- h) OR^4 ,
- 10 i) $O(CH_2)_5 OR^4$,
- j) $CO_2 R^4$,
- k) $(CO)NR^{10}R^{11}$,
- l) $O(CO)NR^{10}R^{11}$,
- m) $N(R^4)(CO)NR^{10}R^{11}$,
- 15 n) $N(R^{10})(CO)R^{11}$,
- o) $N(R^{10})(CO)OR^{11}$,
- p) $SO_2 NR^{10}R^{11}$,
- q) $N(R^{10})SO_2 R^{11}$,
- r) $S(O)_m R^{10}$,
- 20 s) CN ,
- t) $NR^{10}R^{11}$,
- u) $N(R^{10})(CO)NR^4 R^{11}$, and
- v) $O(CO)R^4$;

25 R^1 can be optionally joined to R^2 to form a 4-8 membered ring;

R^2 is independently selected from:

- 1) H, C_0 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 -6 cycloalkyl and heterocycle,
- 30 unsubstituted or substituted with one or more substituents each independently selected from:
 - a) C_{1-6} alkyl,
 - b) C_{3-6} cycloalkyl,

- 5
- c) aryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4 ,
- d) heteroaryl, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
- e) heterocycle, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
- f) $(F)_p C_{1-3}$ alkyl,
- g) halogen,
- h) OR^4 ,
- 10 i) $O(CH_2)_5 OR^4$,
- j) $CO_2 R^4$,
- k) $(CO)NR^{10}R^{11}$,
- l) $O(CO)NR^{10}R^{11}$,
- m) $N(R^4)(CO)NR^{10}R^{11}$,
- 15 n) $N(R^{10})(CO)R^{11}$,
- o) $N(R^{10})(CO)OR^{11}$,
- p) $SO_2 NR^{10}R^{11}$,
- q) $N(R^{10}) SO_2 R^{11}$,
- r) $S(O)_m R^{10}$,
- 20 s) CN ,
- t) $NR^{10}R^{11}$,
- u) $N(R^{10})(CO)NR^4 R^{11}$, and
- v) $O(CO)R^4$,
- 25 2) aryl or heteroaryl, unsubstituted or substituted with one or more substituents each independently selected from:
- a) C_{1-6} alkyl,
- b) C_{3-6} cycloalkyl,
- 30 c) aryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4 ,
- d) heteroaryl, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
- e) heterocycle, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
- 35

- f) $(F)_pC_{1-3}$ alkyl,
- g) halogen,
- h) OR^4 ,
- i) $O(CH_2)_sOR^4$,
- 5 j) CO_2R^4 ,
- k) $(CO)NR^{10}R^{11}$,
- l) $O(CO)NR^{10}R^{11}$,
- m) $N(R^4)(CO)NR^{10}R^{11}$,
- n) $N(R^{10})(CO)R^{11}$,
- 10 o) $N(R^{10})(CO)OR^{11}$,
- p) $SO_2NR^{10}R^{11}$,
- q) $N(R^{10})SO_2R^{11}$,
- r) $S(O)_mR^{10}$,
- s) CN,
- 15 t) $NR^{10}R^{11}$,
- u) $N(R^{10})(CO)NR^4R^{11}$, and
- v) $O(CO)R^4$,

where any two independent R^2 on the same or adjacent atoms optionally join to form a ring selected from cyclobutyl, cyclopentenyl, cyclopentyl, cyclohexenyl, cyclohexyl, phenyl, naphthyl, thienyl, thiazolyl, thiazolinyl, oxazolyl, oxazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, pyrimidyl, pyrazinyl, pyrrolyl, pyrrolinyl, morpholinyl, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S-dioxide, azetidiny, pyrrolidinyl, piperidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridyl, furanyl, dihydrofuranyl, dihydropyranyl and piperazinyl;

R^{10} and R^{11} are each independently selected from: H, C_{1-6} alkyl, $(F)_pC_{1-6}$ alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl, and benzyl, unsubstituted or substituted with halogen, hydroxy or C_{1-6} alkoxy, where R^{10} and R^{11} optionally join to form a ring selected from: azetidiny, pyrrolidinyl, piperidinyl, piperazinyl, and morpholinyl, which is ring is unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ;

R^4 is independently selected from: H, C_{1-6} alkyl, $(F)_pC_{1-6}$ alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl and benzyl, unsubstituted or substituted with halogen, hydroxy or C_{1-6} alkoxy;

W is O, NR^4 or $\text{C}(\text{R}^4)_2$;

X is C or S;

5 Y is O, $(\text{R}^4)_2$, NCN, NSO_2CH_3 or NCONH_2 , or Y is O_2 when X is S;

R^6 is independently selected from H and:

- a) C_{1-6} alkyl,
- 10 b) C_{3-6} cycloalkyl,
- c) aryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4 ,
- d) heteroaryl, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
- 15 e) heterocycle, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
- f) $(\text{F})_p\text{C}_{1-3}$ alkyl,
- g) halogen,
- h) OR^4 .
- 20 i) $\text{O}(\text{CH}_2)_s\text{OR}^4$,
- j) CO_2R^4 ,
- k) $(\text{CO})\text{NR}^{10}\text{R}^{11}$,
- l) $\text{O}(\text{CO})\text{NR}^{10}\text{R}^{11}$,
- m) $\text{N}(\text{R}^4)(\text{CO})\text{NR}^{10}\text{R}^{11}$,
- 25 n) $\text{N}(\text{R}^{10})(\text{CO})\text{R}^{11}$,
- o) $\text{N}(\text{R}^{10})(\text{CO})\text{OR}^{11}$,
- p) $\text{SO}_2\text{NR}^{10}\text{R}^{11}$,
- q) $\text{N}(\text{R}^{10})\text{SO}_2\text{R}^{11}$,
- r) $\text{S}(\text{O})_m\text{R}^{10}$,
- 30 s) CN,
- t) $\text{NR}^{10}\text{R}^{11}$,
- u) $\text{N}(\text{R}^{10})(\text{CO})\text{NR}^4\text{R}^{11}$, and
- v) $\text{O}(\text{CO})\text{R}^4$;

35 J is a bond, $\text{C}(\text{R}^6)_2$, O or NR^6 ;

V is selected from a bond, $C(R^6)_2$, O, $S(O)_m$, NR^6 , $C(R^6)_2-C(R^6)_2$, $C(R^6)=C(R^6)$, $C(R^6)_2-N(R^6)$, $C(R^6)=N$, $N(R^6)-C(R^6)_2$, $N=C(R^6)$, and $N(R^6)-N(R^6)$;

5 G-L is selected from: N, $N-C(R^6)_2$, $C=C(R^6)$, $C=N$, $C(R^6)$, $C(R^6)-C(R^6)_2$, $C(R^6)-C(R^6)_2-C(R^6)_2$, $C=C(R^6)-C(R^6)_2$, $C(R^6)-C(R^6)=C(R^6)$, $C(R^6)-C(R^6)_2-N(R^6)$, $C=C(R^6)-N(R^6)$, $C(R^6)-C(R^6)=N$, $C(R^6)-N(R^6)-C(R^6)_2$, $C=N-C(R^6)_2$, $C(R^6)-N=C(R^6)$, $C(R^6)-N(R^6)-N(R^6)$, $C=N-N(R^6)$, $N-C(R^6)_2-C(R^6)_2$, $N-C(R^6)=C(R^6)$, $N-C(R^6)_2-N(R^6)$, $N-C(R^6)=N$, $N-N(R^6)-C(R^6)_2$ and $N-N=C(R^6)$;

10 Q is selected from:

- (1) $=C(R^{7a})-$,
- (2) $-C(R^{7a})_2-$,
- (3) $-C(=O)-$,
- (4) $-S(O)_m-$,

15 (5) $=N-$, and
(6) $-N(R^{7a})-$;

T is selected from:

- (1) $=C(R^{7b})-$,
- 20 (2) $-C(R^{7b})_2-$,
- (3) $-C(=O)-$,
- (4) $-S(O)_m-$,
- (5) $=N-$, and
- (6) $-N(R^{7b})-$;

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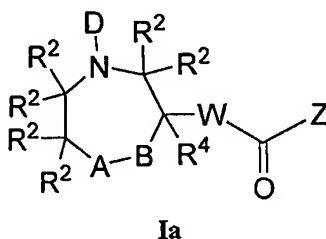
R^3 is independently selected from H, substituted or unsubstituted C_1-C_3 alkyl, F, CN and CO_2R^4 ;

R^{7a} and R^{7b} are each independently selected from R^2 , where R^{7a} and R^{7b} and the atom or atoms to which they are attached optionally join to form a ring selected from C_{3-6} cycloalkyl, aryl, heterocycle, and heteroaryl, which ring is unsubstituted or substituted with 1-10 substituents each independently
30 selected from R^6 ;

p is 0 to $2q+1$, for a substituent with q carbons;
m is 0, 1 or 2;
n is 0 or 1;
s is 1, 2 or 3;

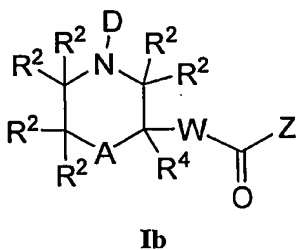
and pharmaceutically acceptable salts and individual diastereomers thereof.

Further embodiments of the invention are CGRP antagonists of Formula I which include
 5 compounds of the Formula Ia:



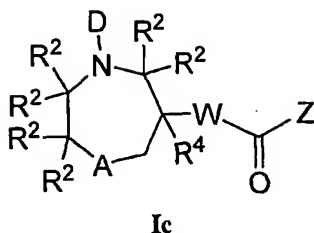
10 wherein:
 A is a bond, $C(R^2)_2$, O, $S(O)_m$ or NR^2 ;
 B is $(C(R^2)_2)_n$;
 n is 0 or 1; and
 D, R^1 , R^2 , R^4 , W, Z, and m are as defined in Formula I;
 15 and pharmaceutically acceptable salts and individual stereoisomers thereof.

Additional embodiments of the invention are CGRP antagonists of Formula I which also
 include compounds of the Formula Ib:



20 wherein:
 A is $C(R^2)_2$, O, $S(O)_m$ or NR^2 ;
 D, R^1 , R^2 , R^4 , W, Z, and m are as defined in Formula I;
 25 and pharmaceutically acceptable salts and individual stereoisomers thereof.

Additional embodiments of the invention are CGRP antagonists of Formula I which
 include compounds of the Formula Ic:



5 wherein:

A is $C(R^2)_2$, O, $S(O)_m$ or NR^2 ;

D, R^1 , R^2 , R^4 , W, Z, and m are defined in Formula I;

and pharmaceutically acceptable salts and individual stereoisomers thereof.

10 Further embodiments of the invention are CGRP antagonists of Formulae Ia –Ic, wherein:

R^1 is selected from:

1) H , C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl and heterocycle, unsubstituted or substituted with one or
15 more substituents each independently selected from:

- a) C_1 - C_6 alkyl,
- b) C_3 - C_6 cycloalkyl,
- c) aryl, unsubstituted or substituted with 1-5 substituents where the substituents are
20 independently selected from R^4 ,
- d) heteroaryl, unsubstituted or substituted with 1-5 substituents each independently
selected from R^4 ,
- e) heterocycle, unsubstituted or substituted with 1-5 substituents each independently
selected from R^4 ,
- f) $(F)_pC_{1-3}$ alkyl,
- g) halogen,
- h) OR^4 .
- i) $O(CH_2)_sOR^4$,
- j) CO_2R^4 .
- 25 k) CN ,
- l) $NR^{10}R^{11}$, and
- m) $O(CO)R^4$, and

30

2) aryl or heteroaryl, unsubstituted or substituted with one or more substituents independently selected from:

- a) C₁₋₆ alkyl,
- 5 b) C₃₋₆ cycloalkyl,
- c) (F)_pC₁₋₃ alkyl,
- d) halogen,
- e) OR⁴,
- f) CO₂R⁴,
- 10 g) (CO)NR¹⁰R¹¹,
- h) SO₂NR¹⁰R¹¹,
- i) N(R¹⁰) SO₂R¹¹,
- j) S(O)_mR⁴,
- k) CN,
- 15 l) NR¹⁰R¹¹, and,
- m) O(CO)R⁴;

R² is selected from:

- 20 1) H, C₀-C₆ alkyl, C₂-C₆ alkynyl, C₃₋₆ cycloalkyl and heterocycle, unsubstituted or substituted with one or more substituents each independently selected from:
- a) C₁₋₆ alkyl,
- b) C₃₋₆ cycloalkyl,
- 25 c) aryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R⁴,
- d) heteroaryl, unsubstituted or substituted with 1-5 substituents each independently selected from R⁴,
- e) heterocycle, unsubstituted or substituted with 1-5 substituents each independently selected from R⁴,
- 30 f) (F)_pC₁₋₃ alkyl,
- g) halogen,
- h) OR⁴,
- i) O(CH₂)_sOR⁴,
- 35 j) CO₂R⁴.

- k) $S(O)_m R^4$,
- l) CN,
- m) $NR^{10}R^{11}$, and
- n) $O(CO)R^4$, and

2) aryl or heteroaryl, unsubstituted or substituted with one more substituents independently selected from:

- a) C₁₋₆ alkyl,
- b) C₃₋₆ cycloalkyl,
- c) (F)_pC₁₋₃ alkyl,
- d) halogen,
- e) OR^4 ,
- f) CO_2R^4 ,
- g) $(CO)NR^{10}R^{11}$,
- h) $SO_2NR^{10}R^{11}$,
- i) $N(R^{10})SO_2R^{11}$,
- j) $S(O)_m R^4$,
- k) CN,
- l) $NR^{10}R^{11}$, and
- m) $O(CO)R^4$,

where any two independent R^2 on the same or adjacent atoms optionally join to form a ring selected from cyclobutyl, cyclopentenyl, cyclopentyl, cyclohexenyl, cyclohexyl, phenyl, naphthyl, thienyl, thiazolyl, thiazolynyl, oxazolyl, oxazolynyl, imidazolyl, imidazolynyl, imidazolidynyl, pyridyl, pyrimidyl, pyrazinyl, pyrrolyl, pyrrolinyl, morpholinyl, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S-dioxide, azetidynyl, pyrrolidinyl, piperidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridyl, furanyl, dihydrofuranyl, dihydropyranyl and piperazinyl;

R^{10} and R^{11} are independently selected from: H, C₁₋₆ alkyl, (F)_pC₁₋₆ alkyl, C₃₋₆ cycloalkyl, aryl, heteroaryl and benzyl, unsubstituted or substituted with halogen, hydroxy or C₁₋₆ alkoxy, where R^{10} and R^{11} optionally join to form a ring selected from: azetidynyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl, which ring is unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ;

R^4 is independently selected from: H, C_{1-6} alkyl, $(F)_p C_{1-6}$ alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl and benzyl, unsubstituted or substituted with halogen, hydroxy or C_1 - C_6 alkoxy;

5 W is O, NR^4 or $C(R^4)_2$;

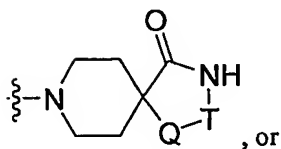
R^6 is independently selected from H and:

- a) C_{1-6} alkyl,
- 10 b) C_{3-6} cycloalkyl,
- c) $(F)_p C_{1-3}$ alkyl,
- d) halogen,
- e) OR^4 ,
- f) CO_2R^4 ,
- 15 g) $(CO)NR^{10}R^{11}$,
- h) $SO_2NR^{10}R^{11}$,
- i) $N(R^{10})SO_2R^{11}$,
- j) $S(O)_mR^4$,
- k) CN,
- 20 l) $NR^{10}R^{11}$ and
- m) $O(CO)R^4$;

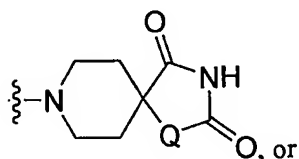
J is a bond, $C(R^5)_2$, O, or NR^5 , and V is a bond, $C(R^6)_2$, O, $S(O)_m$, NR^6 , $C(R^6)_2-C(R^6)_2$, $C(R^6)=C(R^6)$, $C(R^6)_2-N(R^6)$, $C(R^6)=N$, $N(R^6)-C(R^6)_2$, $N=C(R^6)$ or $N(R^6)-N(R^6)$, such that when:

25

J is a bond, V is a bond and Z is Z1 the following structure forms:

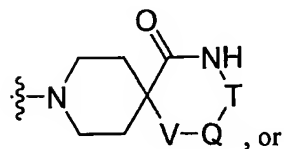


5 J is a bond, V is a bond, Z is Z1 and T is $-C(=O)-$, the following structure forms:



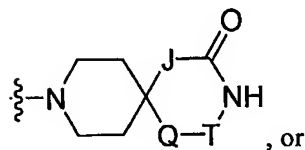
J is a bond and Z is Z1 the following structure forms:

10

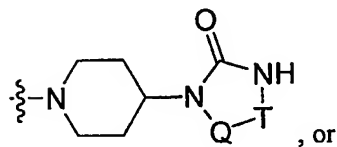


V is a bond and Z is Z1 the following structure forms:

15

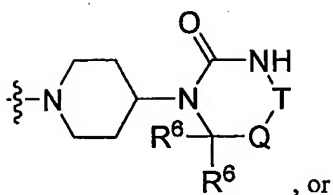


G-L is N, and Z is Z2 the following structure forms:

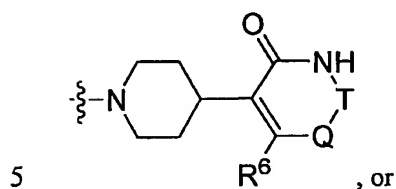


20

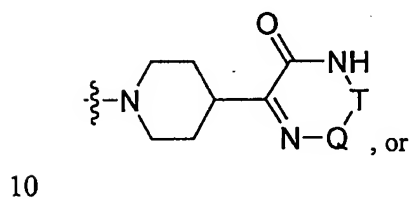
G-L is $N-C(R^6)_2$, and Z is Z2 the following structure forms:



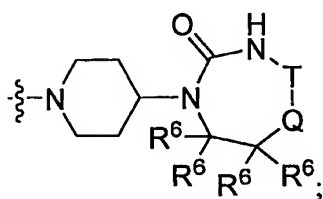
G-L is $C=C(R^6)$, and Z is Z2 the following structure forms:



G-L is $C=N$, and Z is Z2 the following structure forms:



G-L is $N-C(R^6)_2-C(R^6)_2$, and Z is Z2 the following structure forms:



15 Q is selected from:

- (1) $=C(R^{7a})$ -,
- (2) $-C(R^{7a})_2$ -,
- (3) $-C(=O)$ -,
- (4) $-S(O)_m$ -,
- (5) $=N$ -, and
- (6) $-N(R^{7a})$ -;

20

T is selected from:

- (1) $=C(R^{7b})-$,
- (2) $-C(R^{7b})_2-$,
- (3) $-C(=O)-$,
- 5 (4) $-S(O)_m-$,
- (5) $=N-$, and
- (6) $-N(R^{7b})-$;

R^3 is independently selected from H, substituted or unsubstituted C_1 - C_3 alkyl, F, CN and CO_2R^4 ;

- 10 R^{7a} and R^{7b} are each independently selected from R^2 , where R^{7a} and R^{7b} and the atom or atoms to which they are attached optionally join to form a ring selected from C_3 - C_6 cycloalkyl, aryl, heterocycle, and heteroaryl, which ring is unsubstituted or substituted with 1-10 substituents each each independently selected from R^6 ;

p is 0 to $2q+1$, for a substituent with q carbons

15 m is 0 to 2;

s is 1 to 3;

and pharmaceutically acceptable salts and individual stereoisomers thereof.

- 20 Still further embodiments of the invention are CGRP antagonists of Formulae Ia -Ic, wherein:

R^1 is selected from:

- 25 1) H, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl and heterocycle, unsubstituted or substituted with one or more substituents each independently selected from:
- a) C_1 - C_6 alkyl,
 - b) C_3 - C_6 cycloalkyl,
 - 30 c) phenyl, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
 - d) heteroaryl, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
and where heteroaryl is selected from:

imidazole, isoxazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, and thiazole;

e) heterocycle, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 , and where heterocycle is selected from: azetidine, dioxane, dioxolane, morpholine, oxetane, piperazine, piperidine, pyrrolidine, tetrahydrofuran, and tetrahydropyran;

f) $(F)_p C_{1-3}$ alkyl,

g) halogen,

h) OR^4 .

i) $O(CH_2)_s OR^4$,

j) $CO_2 R^4$.

k) CN ,

l) $NR^{10} R^{11}$,

m) $O(CO)R^4$, and

2) aryl or heteroaryl, selected from: phenyl, imidazole, isoxazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, and thiazole, unsubstituted or substituted with one or more substituents each independently selected from:

a) C_{1-6} alkyl,

b) C_{3-6} cycloalkyl,

c) $(F)_p C_{1-3}$ alkyl,

d) halogen,

e) OR^4 .

f) $CO_2 R^4$.

g) $(CO)NR^{10} R^{11}$.

h) $SO_2 NR^{10} R^{11}$.

i) $N(R^{10}) SO_2 R^{11}$.

j) $S(O)_m R^4$,

k) CN ,

l) $NR^{10} R^{11}$, and

m) $O(CO)R^4$;

R^2 is selected from:

- 1) H, C₀-C₆ alkyl, C₃-6 cycloalkyl and heterocycle, unsubstituted or substituted with one or more substituents each independently selected from:

- 5 a) C₁-6 alkyl,
 b) C₃-6 cycloalkyl,
 c) phenyl, unsubstituted or substituted with 1-5 substituents
 each independently selected from R⁴,
 d) heteroaryl, unsubstituted or substituted with 1-5 substituents
 10 each independently selected from R⁴,
 and where heteroaryl is selected from: benzimidazole, benzothiophene, furan,
 imidazole, indole, isoxazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine,
 pyrimidine, pyrrole, thiazole, thiophene, and triazole;
 e) heterocycle, unsubstituted or substituted with 1-5 substituents where the
 15 substituents are independently selected from R⁴, and where heterocycle is
 selected from: azetidine, imidazolidine, imidazoline, isoxazoline, isoxazolidine,
 morpholine, oxazoline, oxazolidine, oxetane, pyrazolidine, pyrazoline, pyrroline,
 tetrahydrofuran, tetrahydropyran, thiazoline, and thiazolidine;
 f) (F)_pC₁₋₃ alkyl,
 20 g) halogen,
 h) OR⁴.
 i) O(CH₂)_sOR⁴.
 j) CO₂R⁴.
 k) CN,
 25 l) NR¹⁰R¹¹, and
 m) O(CO)R⁴, and

- 2) aryl or heteroaryl, selected from:
 phenyl, benzimidazole, benzothiophene, furan, imidazole, indole, isoxazole, oxazole,
 30 pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, thiazole, thiophene, and
 triazole, unsubstituted or substituted with one or more substituents each independently
 selected from:

- 35 a) C₁-6 alkyl,
 b) C₃-6 cycloalkyl,

- c) (F)_pC₁₋₃ alkyl,
 d) halogen,
 e) OR⁴,
 f) CO₂R⁴,
 5 g) (CO)NR¹⁰R¹¹,
 h) SO₂NR¹⁰R¹¹,
 i) N(R¹⁰)SO₂R¹¹,
 j) S(O)_mR⁴,
 k) CN,
 10 l) NR¹⁰R¹¹, and
 m) O(CO)R⁴,

where any two independent R² on the same or adjacent atoms optionally join to form a ring
 selected from cyclobutyl, cyclopentenyl, cyclopentyl, cyclohexenyl, cyclohexyl, phenyl,
 15 naphthyl, thienyl, thiazolyl, thiazolinyl, oxazolyl, oxazolinyl, imidazolyl, imidazolinyl,
 imidazolidinyl, pyridyl, pyrimidyl, pyrazinyl, pyrrolyl, pyrrolinyl, morpholinyl, thiomorpholine,
 thiomorpholine S-oxide, thiomorpholine S-dioxide, azetidyl, pyrrolidinyl, piperidinyl,
 tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridyl, furanyl, dihydrofuranyl, dihydropyranyl
 and piperazinyl,

20 R¹⁰ and R¹¹ are independently selected from: H, C₁₋₆ alkyl, (F)_pC₁₋₆ alkyl, C₃₋₆ cycloalkyl, aryl,
 heteroaryl and benzyl, unsubstituted or substituted with halogen, hydroxy or C_{1-C6} alkoxy, where R¹⁰
 and R¹¹ optionally join to form a ring selected from: azetidyl, pyrrolidinyl, piperidinyl, piperazinyl and
 morpholinyl, which ring is unsubstituted or substituted with 1-5 substituents each independently selected
 25 from R⁴;

R⁴ is independently selected from: H, C₁₋₆ alkyl, (F)_pC₁₋₆ alkyl, C₃₋₆ cycloalkyl, aryl, heteroaryl and
 phenyl, unsubstituted or substituted with hydroxy or C_{1-C6} alkoxy;

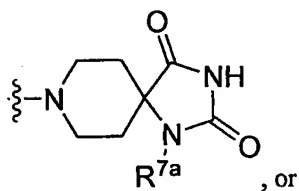
30 W is NR⁴ or C(R⁴)₂;

R⁶ is independently selected from H and:

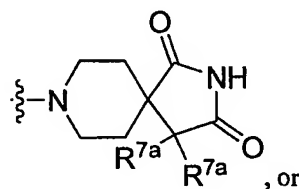
- 35 a) C₁₋₆ alkyl,
 b) C₃₋₆ cycloalkyl,

- c) $(F)_p C_{1-3}$ alkyl,
- d) halogen,
- e) OR^4 ,
- f) CO_2R^4 ,
- g) $(CO)NR^{10}R^{11}$,
- h) $SO_2NR^{10}R^{11}$,
- i) $N(R^{10})SO_2R^{11}$,
- j) $S(O)_mR^4$,
- k) CN,
- l) $NR^{10}R^{11}$, and
- m) $O(CO)R^4$;

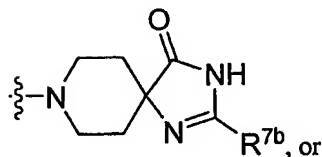
J is a bond, V is a bond, Z is Z1, Q is $-N(R^{7a})-$, and T is $-C(=O)-$, such that the following structure forms:



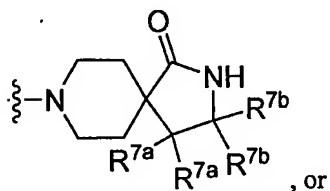
J is a bond, V is a bond, Z is Z1, Q is $-C(R^{7a})_2-$, and T is $-C(=O)-$, such that the following structure forms:



J is a bond, V is a bond, Z is Z1, Q is $-N=$, and T is $=C(R^{7b})-$, such that the following structure forms:

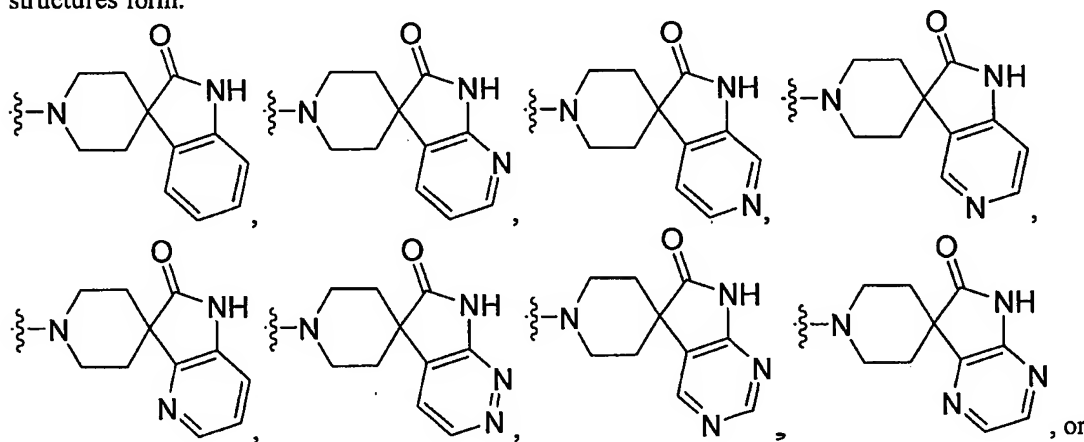


J is a bond, V is a bond, Z is Z1, Q is $-C(R^{7a})_2$, and T is $-C(R^{7b})_2$, such that the following structure forms:



5

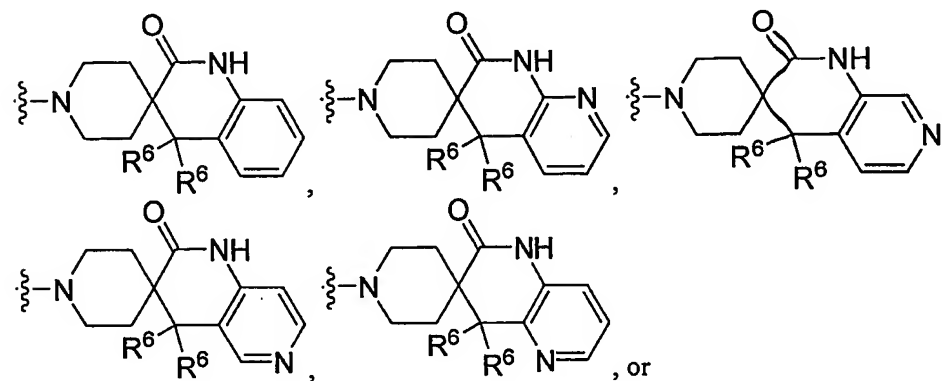
J is a bond, V is a bond, Z is Z1, Q is $-C(R^{7a})_2$, T is $=C(R^{7b})_2$, and the atoms to which R^{7a} and R^{7b} are attached are joined together to form a benzene, pyridine, or diazine ring such that one of the following structures form:



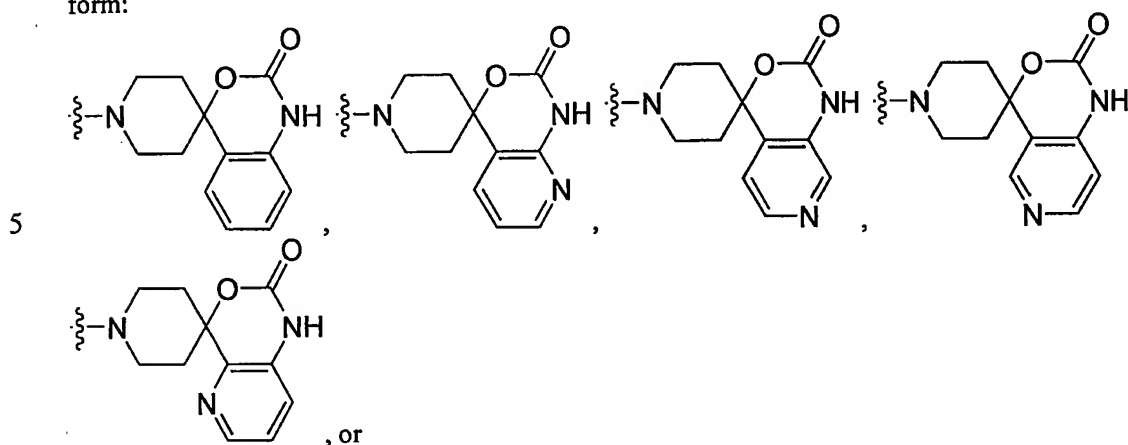
10

J is a bond, V is $C(R^6)_2$, Z is Z1, Q is $-C(R^{7a})_2$, T is $=C(R^{7b})_2$, and the atoms to which R^{7a} and R^{7b} are attached are joined together to form a benzene, or pyridine ring such that one of the following structures form:

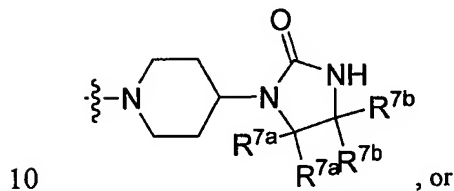
15



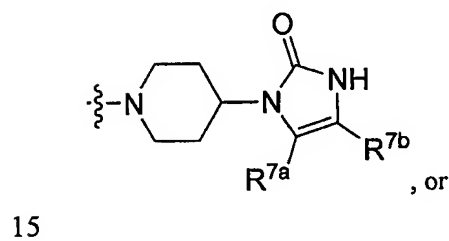
J is O, V is a bond, Z is Z1, Q is $-C(R^{7a})=$, T is $=C(R^{7b})-$, and the atoms to which R^{7a} and R^{7b} are attached are joined together to form a benzene, or pyridine ring such that one of the following structures form:



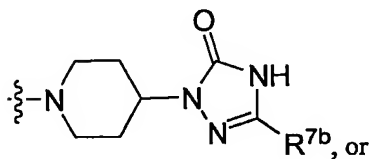
G-L is N, Z is Z2, Q is $-C(R^{7a})_2-$, and T is $-C(R^{7b})_2-$, such that the following structure forms:



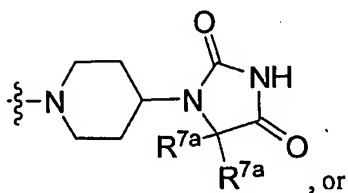
G-L is N, Z is Z2, Q is $-C(R^{7a})=$ and T is $=C(R^{7b})-$ such that the following structure forms:



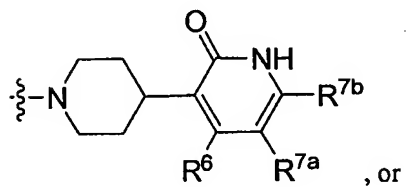
G-L is N, Z is Z2, Q is $-N=$, and T is $=C(R^{7b})-$, such that the following structure forms:



G-L is N, Z is Z2, Q is $-C(R^{7a})_2-$, and T is $-C(O)-$, such that the following structure forms:

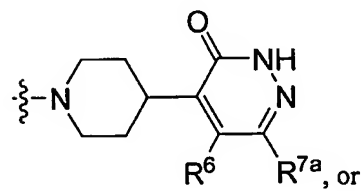


5 G-L is $C=C(R^6)$, Z is Z2, Q is $-C(R^{7a})=$ and T is $=C(R^{7b})-$, such that the following structure forms:

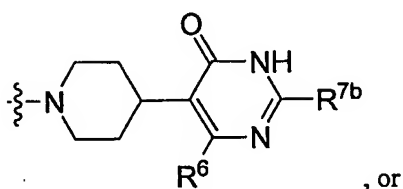


G-L is $C=C(R^6)$, Z is Z2, Q is $-C(R^{7a})=$ and T is $=N-$, such that the following structure forms:

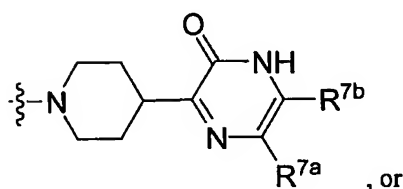
10



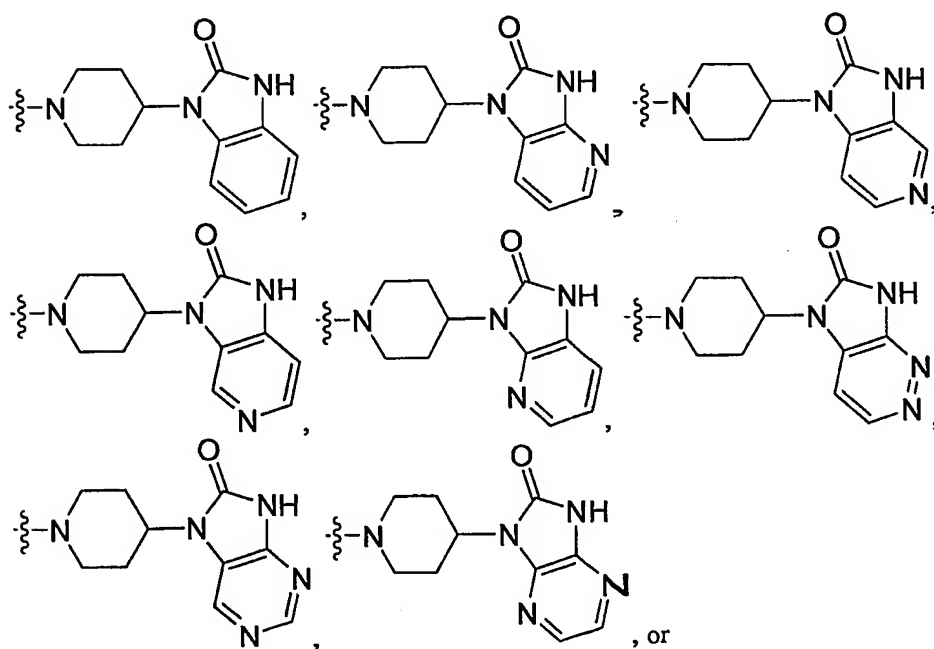
G-L is $C=C(R^6)$, Z is Z2, Q is $-N=$ and T is $=C(R^{7b})-$, such that the following structure forms:



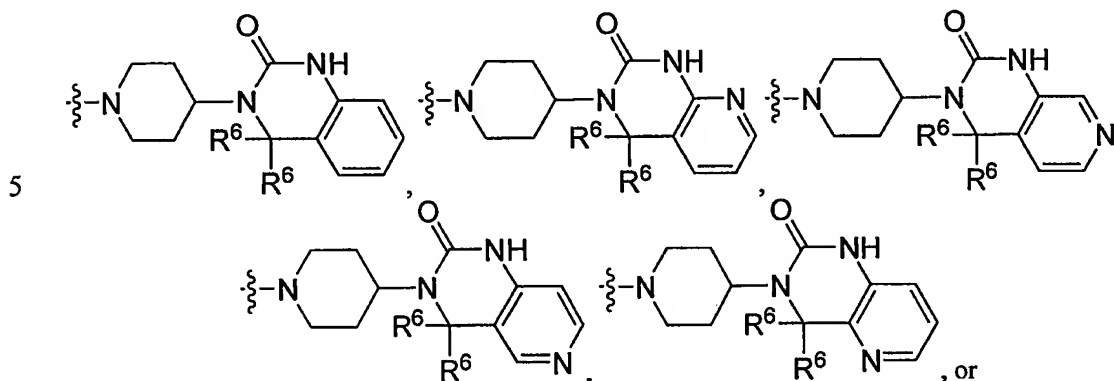
5 G-L is $C=N$, Z is Z2, Q is $-C(R^{7a})=$ and T is $=C(R^{7b})-$, such that the following structure forms:



10 G-L is N, Z is Z2, Q is $-C(R^{7a})=$, and T is $=C(R^{7b})-$, and the atoms to which R^{7a} and R^{7b} are attached are joined together to form a benzene, pyridine, or diazine ring such that one of the following structures form:

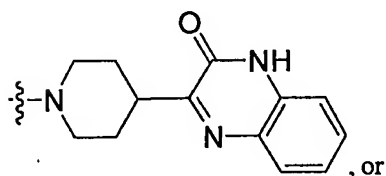


G-L is $N-C(R^6)_2$, Z is Z2, Q is $-C(R^{7a})=$, and T is $=C(R^{7b})-$, and the atoms to which R^{7a} and R^{7b} are attached are joined together to form a benzene, or pyridine ring such that one of the following structures form:



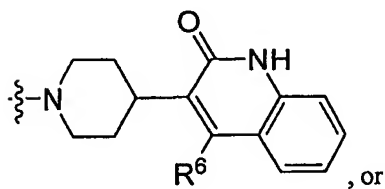
G-J is $C=N$, Z is Z2, Q is $-C(R^{7a})=$, and T is $=C(R^{7b})-$, and the atoms to which R^{7a} and R^{7b} are attached are joined together to form a benzene ring such that the following structure forms:

10



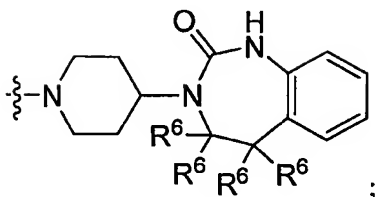
G-L is $C=C(R^6)$, Z is Z2, Q is $-C(R^{7a})=$, and T is $=C(R^{7b})-$, and the atoms to which R^{7a} and R^{7b} are attached are joined together to form a benzene ring such that the following structure forms:

15



G-L is $N-C(R^6)_2-C(R^6)_2$, Z is Z2, Q is $-C(R^{7a})=$, and T is $=C(R^{7b})-$, and the atoms to which R^{7a} and R^{7b} are attached are joined together to form a benzene ring such that the following structure forms:

20



R^3 is independently selected from H, substituted or unsubstituted C_1 - C_3 alkyl, F, CN and CO_2R^4 ;

R^{7a} and R^{7b} are each independently selected from R^2 , where R^{7a} and R^{7b} and the atom or atoms to which they are attached optionally join to form a ring selected from C_{3-6} cycloalkyl, aryl, heterocycle, and heteroaryl which is unsubstituted or substituted with 1-10 substituents each each independently selected from R^6 ;

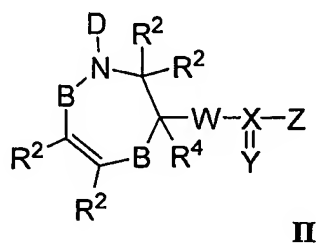
p is 0 to $2q+1$, for a substituent with q carbons

m is 0 to 2;

s is 1 to 3;

and pharmaceutically acceptable salts and individual stereoisomers thereof.

Another embodiment of the invention includes CGRP antagonists which include compounds of Formula II:



wherein:

D, B, W, X, Y, Z, R^2 and R^4 are as defined in Formula I, and pharmaceutically acceptable salts and individual diastereomers thereof.

It is to be understood that where one or more of the above recited structures or substructures recite multiple substituents having the same designation each such variable may be the same or different from each similarly designated variable. For example, R^2 is recited four times in Formula I,

and each R² in Formula I may independently be any of the substructures defined under R². The invention is not limited to structures and substructures wherein each R² must be the same for a given structure. The same is true with respect to any variable appearing multiple time in a structure or substructure.

5 The compounds of the present invention may contain one or more asymmetric centers and can thus occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. Additional asymmetric centers may be present depending upon the nature of the various substituents on the molecule. Each such asymmetric center will independently produce two optical isomers and it is intended that all of the possible optical isomers and diastereomers in mixtures
10 and as pure or partially purified compounds are included within the ambit of this invention. The present invention is meant to comprehend all such isomeric forms of these compounds.

 Some of the compounds described herein contain olefinic double bonds, and unless specified otherwise, are meant to include both E and Z geometric isomers.

 The independent syntheses of these diastereomers or their chromatographic separations
15 may be achieved as known in the art by appropriate modification of the methodology disclosed herein. Their absolute stereochemistry may be determined by the x-ray crystallography of crystalline products or crystalline intermediates which are derivatized, if necessary, with a reagent containing an asymmetric center of known absolute configuration.

 If desired, racemic mixtures of the compounds may be separated so that the individual
20 enantiomers are isolated. The separation can be carried out by methods well known in the art, such as the coupling of a racemic mixture of compounds to an enantiomerically pure compound to form a diastereomeric mixture, followed by separation of the individual diastereomers by standard methods, such as fractional crystallization or chromatography. The coupling reaction is often the formation of salts using an enantiomerically pure acid or base. The diastereomeric derivatives may then be converted to the
25 pure enantiomers by cleavage of the added chiral residue. The racemic mixture of the compounds can also be separated directly by chromatographic methods utilizing chiral stationary phases, which methods are well known in the art.

 Alternatively, any enantiomer of a compound may be obtained by stereoselective synthesis using optically pure starting materials or reagents of known configuration by methods well
30 known in the art.

 As will be appreciated by those of skill in the art, not every substituent or combination of substituents which are said to form rings are capable of forming a ring structure in every circumstance or situation. Moreover, even those substituents capable of ring formation may or may not form a ring structure in every circumstance or situation.

Also as appreciated by those of skill in the art, halo or halogen as used herein are intended to include chloro, fluoro, bromo and iodo.

As used herein, "alkyl" is intended to mean linear, branched and cyclic structures having no double or triple bonds. Thus C₁₋₆alkyl is defined to identify the group as having 1, 2, 3, 4, 5 or 6
5 carbons in a linear or branched arrangement, such that C₁₋₆alkyl specifically includes methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl and hexyl. "Cycloalkyl" is an alkyl, part or all of which which forms a ring of three or more atoms. C₀ or C₀alkyl is defined to identify the presence of a direct covalent bond.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring
10 of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, or biphenyl.

The term "heterocycle" or "heterocyclic", as used herein except where noted, represents a stable 5- to 7-membered monocyclic- or stable 8- to 11-membered bicyclic heterocyclic ring system which is either saturated or unsaturated, and which consists of carbon atoms and from one to four
15 heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic groups include, but are not limited to,
20 azetidine, chroman, dihydrofuran, dihydropyran, dioxane, dioxolane, hexahydroazepine, imidazolidine, imidazolidinone, imidazoline, imidazolinone, indoline, isochroman, isoindoline, isothiazoline, isothiazolidine, isoxazoline, isoxazolidine, morpholine, morpholinone, oxazoline, oxazolidine, oxazolidinone, oxetane, 2-oxohexahydroazepin, 2-oxopiperazine, 2-oxopiperidine, 2-oxopyrrolidine, piperazine, piperidine, pyran, pyrazolidine, pyrazoline, pyrrolidine, pyrroline, quinuclidine,
25 tetrahydrofuran, tetrahydropyran, thiamorpholine, thiazoline, thiazolidine, thiomorpholine and N-oxides thereof.

The term "heteroaryl", as used herein except where noted, represents a stable 5- to 7-membered monocyclic- or stable 9- to 10-membered fused bicyclic heterocyclic ring system which contains an aromatic ring, any ring of which may be saturated, such as piperidinyl, partially saturated, or
30 unsaturated, such as pyridinyl, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O and S, and wherein the nitrogen and sulfur heteroatoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a
35 stable structure. Examples of such heteroaryl groups include, but are not limited to, benzimidazole,

benzothiazole, benzisoxazole, benzofuran, benzothiazole, benzothiophene, benzotriazole, benzoxazole, carboline, cinnoline, furan, furazan, imidazole, indazole, indole, indolizine, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, phthalazine, pteridine, purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, quinazoline, quinoline, quinoxaline, tetrazole, thiazole, thiadiazole, thiophene, triazine, triazole, and N-oxides thereof.

The term "alkoxy," as in C₁-C₆ alkoxy, is intended to refer to include alkoxy groups of from 1 to 6 carbon atoms of a straight, branched and cyclic configuration. Examples include methoxy, ethoxy, propoxy, isopropoxy, cyclopropyloxy, cyclohexyloxy and the like.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The number of certain variables present in certain instances is defined in terms of the number of carbons present. For example, variable "p" is occasionally defined as follows: "p is 0 to 2q+1, for a substituent with q carbons". Where the substituent is "(F)_pC₁₋₃ alkyl" this means that when there is one carbon, there are 2(1) + 1 = 3 fluorines. When there are two carbons, there are 2(2) + 1 = 5 fluorines, and when there are three carbons there are 2(3) + 1 = 7 fluorines.

When variables G and L are presented or depicted as "G-L" this indicates that G and L together represent a particular moiety. G-L may represent a single ring atom or various arrangements of multiple ring atoms. For instance, G-L is at times herein defined as the single ring atom N, and is at other times defined as multiple ring atoms N-C(R⁶)₂, C=C(R⁶), and so forth.

When the compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids, including inorganic and organic acids. Such acids include

acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, malic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic acid, and the like. In one aspect of the invention the salts are citric, hydrobromic, hydrochloric, maleic, phosphoric, sulfuric, fumaric, and tartaric acids. It will be understood that, as used herein, references to the compounds of Formula I are meant to also include the pharmaceutically acceptable salts.

Exemplifying the invention is the use of the compounds disclosed in the Examples and herein. Specific compounds within the present invention include a compound which selected from the group consisting of the compounds disclosed in the following Examples and pharmaceutically acceptable salts thereof and individual diastereomers thereof.

The subject compounds are useful in a method of antagonism of CGRP receptors in a patient such as a mammal in need of such antagonism comprising the administration of an effective amount of the compound. The present invention is directed to the use of the compounds disclosed herein as antagonists of CGRP receptors. In addition to primates, especially humans, a variety of other mammals can be treated according to the method of the present invention.

Another embodiment of the present invention is directed to a method for the treatment, control, amelioration, or reduction of risk of a disease or disorder in which the CGRP receptor is involved in a patient that comprises administering to the patient a therapeutically effective amount of a compound that is an antagonist of CGRP receptors.

The present invention is further directed to a method for the manufacture of a medicament for antagonism of CGRP receptors activity in humans and animals comprising combining a compound of the present invention with a pharmaceutical carrier or diluent.

The subject treated in the present methods is generally a mammal, for example a human being, male or female, in whom antagonism of CGRP receptor activity is desired. The term "therapeutically effective amount" means the amount of the subject compound that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician. As used herein, the term "treatment" refers both to the treatment and to the prevention or prophylactic therapy of the mentioned conditions, particularly in a patient who is predisposed to such disease or disorder.

The term "composition" as used herein is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. Such term in relation to pharmaceutical composition, is intended to encompass a product comprising the active ingredient(s), and the inert ingredient(s) that make up the carrier, as well as any product which results, directly or indirectly, from combination, complexation or aggregation of any two or more of the ingredients, or from

dissociation of one or more of the ingredients, or from other types of reactions or interactions of one or more of the ingredients. Accordingly, the pharmaceutical compositions of the present invention encompass any composition made by admixing a compound of the present invention and a pharmaceutically acceptable carrier. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The terms "administration of" and or "administering a" compound should be understood to mean providing a compound of the invention or a prodrug of a compound of the invention to the individual in need of treatment.

The utility of the compounds in accordance with the present invention as antagonists of CGRP receptor activity may be demonstrated by methodology known in the art. Inhibition of the binding of ^{125}I -CGRP to receptors and functional antagonism of CGRP receptors were determined as follows:

NATIVE RECEPTOR BINDING ASSAY: The binding of ^{125}I -CGRP to receptors in SK-N-MC cell membranes was carried out essentially as described (Edvinsson *et al.* (2001) *Eur. J. Pharmacol.* **415**, 39-44). Briefly, membranes (25 μg) were incubated in 1 ml of binding buffer [10 mM HEPES, pH 7.4, 5 mM MgCl_2 and 0.2% bovine serum albumin (BSA)] containing 10 pM ^{125}I -CGRP and antagonist. After incubation at room temperature for 3 h, the assay was terminated by filtration through GFB glass fibre filter plates (Millipore) that had been blocked with 0.5% polyethyleneimine for 3 h. The filters were washed three times with ice-cold assay buffer, then the plates were air dried. Scintillation fluid (50 μl) was added and the radioactivity was counted on a Topcount (Packard Instrument). Data analysis was carried out by using Prism and the K_i was determined by using the Cheng-Prusoff equation (Cheng & Prusoff (1973) *Biochem. Pharmacol.* **22**, 3099-3108).

NATIVE RECEPTOR FUNCTIONAL ASSAY: SK-N-MC cells were grown in minimal essential medium (MEM) supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 0.1 mM non-essential amino acids, 1 mM sodium pyruvate, 100 units/ml penicillin and 100 $\mu\text{g}/\text{ml}$ streptomycin at 37 $^\circ\text{C}$, 95% humidity, and 5% CO_2 . For cAMP assays, cells were plated at 5×10^5 cells/well in 96-well poly-D-lysine-coated plates (Becton-Dickinson) and cultured for ~ 18 h before assay. Cells were washed with phosphate-buffered saline (PBS, Sigma) then pre-incubated with 300 μM isobutylmethylxanthine in serum-free MEM for 30 min at 37 $^\circ\text{C}$. Antagonist was added and the cells were incubated for 10 min before the addition of CGRP. The incubation was continued for another 15 min, then the cells were washed with PBS and processed for cAMP determination according to the manufacturer's recommended protocol. Maximal stimulation over basal was defined by using 100 nM CGRP. Dose-response curves were generated by using Prism. Dose-ratios (DR) were calculated and used to construct full Schild plots (Arunlakshana & Schild (1959) *Br. J. Pharmacol.* **14**, 48-58).

RECOMBINANT RECEPTOR: Human CRLR (Genbank accession number L76380) was subcloned into the expression vector pIRESHyg2 (BD Biosciences Clontech) as a 5'NheI and 3' PmeI fragment. Human RAMP1 (Genbank accession number AJ001014) was subcloned into the expression vector pRESpuo2 (BD Biosciences Clontech) as a 5'NheI and 3'NotI fragment. 293 cells (human embryonic kidney cells; ATCC #CRL-1573) were cultured in DMEM with 4.5 g/L glucose, 1 mM sodium pyruvate and 2 mM glutamine supplemented with 10% fetal bovine serum (FBS), 100 units/mL penicillin and 100 ug/ml streptomycin, and maintained at 37°C and 95% humidity. Cells were subcultured by treatment with 0.25% trypsin with 0.1% EDTA in HBSS. Stable cell line generation was accomplished by co-transfecting 10 ug of DNA with 30 ug Lipofectamine 2000 (Invitrogen) in 75 cm² flasks. CRLR and RAMP1 expression constructs were co-transfected in equal amounts. Twenty-four hours after transfection the cells were diluted and selective medium (growth medium + 300 ug/ml hygromycin and 1 ug/ml puromycin) was added the following day. A clonal cell line was generated by single cell deposition utilizing a FACS Vantage SE (Becton Dickinson). Growth medium was adjusted to 150 ug/ml hygromycin and 0.5 ug/ml puromycin for cell propagation.

RECOMBINANT RECEPTOR BINDING ASSAY: Cells expressing recombinant human CRLR/RAMP1 were washed with PBS and harvested in harvest buffer containing 50 mM HEPES, 1 mM EDTA and Complete protease inhibitors (Roche). The cell suspension was disrupted with a laboratory homogenizer and centrifuged at 48,000 g to isolate membranes. The pellets were resuspended in harvest buffer plus 250 mM sucrose and stored at -70°C. For binding assays, 10 ug of membranes were incubated in 1 ml binding buffer (10 mM HEPES, pH 7.4, 5 mM MgCl₂, and 0.2% BSA) for 3 hours at room temperature containing 10 pM ¹²⁵I-hCGRP (Amersham Biosciences) and antagonist. The assay was terminated by filtration through 96-well GFB glass fiber filter plates (Millipore) that had been blocked with 0.05% polyethyleneimine. The filters were washed 3 times with ice-cold assay buffer (10 mM HEPES, pH 7.4). Scintillation fluid was added and the plates were counted on a Topcount (Packard). Non-specific binding was determined and the data analysis was carried out with the apparent dissociation constant (K_i) determined by using a non-linear least squares fitting the bound CPM data to the equation below:

$$Y_{\text{obsd}} = \frac{(Y_{\text{max}} - Y_{\text{min}})(\%I_{\text{max}} - \%I_{\text{min}} / 100) + Y_{\text{min}} + (Y_{\text{max}} - Y_{\text{min}})(100 - \%I_{\text{max}} / 100)}{1 + ([\text{Drug}] / K_i (1 + [\text{Radiolabel}] / K_d))^n}$$

Where Y is observed CPM bound, Y_{max} is total bound counts, Y min is non specific bound counts, (Y max - Y min) is specific bound counts, % I max is the maximum percent inhibition, % I min is the minimum percent inhibition, radiolabel is the probe, and the K_d is the apparent dissociation constant for the radioligand for the receptor as determined by Hot saturation experiments.

RECOMBINANT RECEPTOR FUNCTIONAL ASSAY: Cells were plated in complete growth medium at 85,000 cells/well in 96-well poly-D-lysine coated plates (Corning) and cultured for ~

19 h before assay. Cells were washed with PBS and then incubated with inhibitor for 30 min at 37°C and 95% humidity in Cellgro Complete Serum-Free/Low-Protein medium (Mediatech, Inc.) with L-glutamine and 1 g/L BSA. Isobutyl-methylxanthine was added to the cells at a concentration of 300 µM and incubated for 30 min at 37°C. Human α-CGRP was added to the cells at a concentration of 0.3 nM and allowed to incubate at 37°C for 5 min. After α-CGRP stimulation the cells were washed with PBS and processed for cAMP determination utilizing the two-stage assay procedure according to the manufacturer's recommended protocol (cAMP SPA direct screening assay system; RPA 559; Amersham Biosciences). Dose response curves were plotted and IC₅₀ values determined from a 4-parameter logistic fit as defined by the equation $y = ((a-d)/(1+(x/c)^b) + d$, where y = response, x = dose, a = max response, d = min response, c = inflection point and b = slope.

In particular, the compounds of the following examples had activity as antagonists of the CGRP receptor in the aforementioned assays, generally with a K_i or IC₅₀ value of less than about 50 µM. Such a result is indicative of the intrinsic activity of the compounds in use as antagonists of CGRP receptors.

The ability of the compounds of the present invention to act as CGRP antagonists makes them useful pharmacological agents for disorders that involve CGRP in humans and animals, but particularly in humans.

The compounds of the present invention have utility in treating, preventing, ameliorating, controlling or reducing the risk of one or more of the following conditions or diseases: headache; migraine; cluster headache; chronic tension type headache; pain; chronic pain; neurogenic inflammation and inflammatory pain; neuropathic pain; eye pain; tooth pain; diabetes; non-insulin dependent diabetes mellitus; vascular disorders; inflammation; arthritis; bronchial hyperreactivity; asthma; shock; sepsis; opiate withdrawal syndrome; morphine tolerance; hot flashes in men and women; allergic dermatitis; psoriasis; encephalitis; brain trauma; epilepsy; neurodegenerative diseases; skin diseases; neurogenic cutaneous redness, skin rosaceousness and erythema; inflammatory bowel disease, irritable bowel syndrome, cystitis; and other conditions that may be treated or prevented by antagonism of CGRP receptors. Of particular importance is the acute or prophylactic treatment of headache, including migraine and cluster headache.

The subject compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the diseases, disorders and conditions noted herein.

The subject compounds are further useful in a method for the prevention, treatment, control, amelioration, or reduction of risk of the aforementioned diseases, disorders and conditions in combination with other agents.

The compounds of the present invention may be used in combination with one or more other drugs in the treatment, prevention, control, amelioration, or reduction of risk of diseases or

conditions for which compounds of Formula I or the other drugs may have utility, where the combination of the drugs together are safer or more effective than either drug alone. Such other drug(s) may be administered, by a route and in an amount commonly used therefor, contemporaneously or sequentially with a compound of Formula I. When a compound of Formula I is used contemporaneously with one or more other drugs, a pharmaceutical composition in unit dosage form containing such other drugs and the compound of Formula I is preferred. However, the combination therapy may also include therapies in which the compound of Formula I and one or more other drugs are administered on different overlapping schedules. It is also contemplated that when used in combination with one or more other active ingredients, the compounds of the present invention and the other active ingredients may be used in lower doses than when each is used singly. Accordingly, the pharmaceutical compositions of the present invention include those that contain one or more other active ingredients, in addition to a compound of Formula I.

For example, the present compounds may be used in conjunction with an anti-migraine agent, such as ergotamine and dihydroergotamine, or other serotonin agonists, especially a 5-HT_{1B/1D} agonist, for example sumatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan, donitriptan, and rizatriptan, a 5-HT_{1D} agonist such as PNU-142633 and a 5-HT_{1F} agonist such as LY334370; a cyclooxygenase inhibitor, such as a selective cyclooxygenase-2 inhibitor, for example rofecoxib, etoricoxib, celecoxib, valdecoxib or paracoxib; a non-steroidal anti-inflammatory agent or a cytokine-suppressing anti-inflammatory agent, for example with a compound such as ibuprofen, ketoprofen, fenoprofen, naproxen, indomethacin, sulindac, meloxicam, piroxicam, tenoxicam, lornoxicam, ketorolac, etodolac, mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid, diclofenac, oxaprozin, apazone, nimesulide, nabumetone, tenidap, etanercept, tolmetin, phenylbutazone, oxyphenbutazone, diflunisal, salsalate, olsalazine or sulfasalazine and the like; or glucocorticoids. Similarly, the instant compounds may be administered with an analgesic such as aspirin, acetaminophen, phenacetin, fentanyl, sufentanil, methadone, acetyl methadol, buprenorphine or morphine.

Additionally, the present compounds may be used in conjunction with an interleukin inhibitor, such as an interleukin-1 inhibitor; an NK-1 receptor antagonist, for example aprepitant; an NMDA antagonist; an NR2B antagonist; a bradykinin-1 receptor antagonist; an adenosine A1 receptor agonist; a sodium channel blocker, for example lamotrigine; an opiate agonist such as levomethadyl acetate or methadyl acetate; a lipoxygenase inhibitor, such as an inhibitor of 5-lipoxygenase; an alpha receptor antagonist, for example indoramin; an alpha receptor agonist; a vanilloid receptor antagonist; a renin inhibitor; a granzyme B inhibitor; a substance P antagonist; an endothelin antagonist; a norepinephrin precursor; anti-anxiety agents such as diazepam, alprazolam, chlordiazepoxide and chlorazepate; serotonin 5HT₂ receptor antagonists; opioid agonists such as codeine, hydrocodone, tramadol, dextropropoxyphene and fentanyl; an mGluR5 agonist, antagonist or potentiator; a GABA A

receptor modulator, for example acamprosate calcium; nicotinic antagonists or agonists including nicotine; muscarinic agonists or antagonists; a selective serotonin reuptake inhibitor, for example fluoxetine, paroxetine, sertraline, duloxetine, escitalopram, or citalopram; an antidepressant, for example amitriptyline, nortriptyline, clomipramine, imipramine, venlafaxine, doxepin, protriptyline, desipramine, trimipramine, or imipramine; a leukotriene antagonist, for example montelukast or zafirlukast; an inhibitor of nitric oxide or an inhibitor of the synthesis of nitric oxide.

Also, the present compounds may be used in conjunction with gap junction inhibitors; neuronal calcium channel blockers such as civamide; AMPA/KA antagonists such as LY293558; sigma receptor agonists; and vitamin B2.

Also, the present compounds may be used in conjunction with ergot alkaloids other than ergotamine and dihydroergotamine, for example ergonovine, ergonovine, methylegonovine, metergoline, ergoloid mesylates, dihydroergocornine, dihydroergocristine, dihydroergocryptine, dihydro- α -ergocryptine, dihydro- β -ergocryptine, ergotoxine, ergocornine, ergocristine, ergocryptine, α -ergocryptine, β -ergocryptine, ergosine, ergostane, bromocriptine, or methysergide.

Additionally, the present compounds may be used in conjunction with a beta-adrenergic antagonist such as timolol, propranolol, atenolol, metoprolol or nadolol, and the like; a MAO inhibitor, for example phenelzine; a calcium channel blocker, for example flunarizine, diltiazem, amlodipine, felodipine, nisoldipine, isradipine, nimodipine, lomerizine, verapamil, nifedipine, or prochlorperazine; neuroleptics such as olanzapine, droperidol, prochlorperazine, chlorpromazine and quetiapine; an anticonvulsant such as topiramate, zonisamide, tonabersat, carbamazepine, levetiracetam, lamotrigine, tiagabine, gabapentin, pregabalin or divalproex sodium; an anti-hypertensive such as an angiotensin II antagonist, for example losartan, irbesartan, valsartan, eprosartan, telmisartan, olmesartan, medoxomil, candesartan and candesartan cilexetil, an angiotensin I antagonist, an angiotensin converting enzyme inhibitor such as lisinopril, enalapril, captopril, benazepril, quinapril, perindopril, ramipril andtrandolapril; or botulinum toxin type A or B.

The present compounds may be used in conjunction with a potentiator such as caffeine, an H2-antagonist, simethicone, aluminum or magnesium hydroxide; a decongestant such as oxymetazoline, epinephrine, naphazoline, xylometazoline, propylhexedrine, or levo-desoxy-ephedrine; an antitussive such as caramiphen, carbetapentane, or dextromethorphan; a diuretic; a prokinetic agent such as metoclopramide or domperidone; a sedating or non-sedating antihistamine such as acrivastine, azatadine, bromodiphenhydramine, brompheniramine, carbinoxamine, chlorpheniramine, clemastine, dextbrompheniramine, dexchlorpheniramine, diphenhydramine, doxylamine, loratadine, phenindamine, pheniramine, phenyltoloxamine, promethazine, pyrilamine, terfenadine, triprolidine, phenylephrine, phenylpropanolamine, or pseudoephedrine. The present compounds also may be used in conjunction with anti-emetics.

In a particularly preferred embodiment the present compounds are used in conjunction with an anti-migraine agent, such as: ergotamine or dihydroergotamine; a 5-HT₁ agonist, especially a 5-HT_{1B/1D} agonist, in particular, sumatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, frovatriptan, donitriptan, avitriptan and rizatriptan, and other serotonin agonists; and a cyclooxygenase inhibitor, such as a selective cyclooxygenase-2 inhibitor, in particular, rofecoxib, etoricoxib, celecoxib, valdecoxib or paracoxib.

The above combinations include combinations of a compound of the present invention not only with one other active compound, but also with two or more other active compounds. Likewise, compounds of the present invention may be used in combination with other drugs that are used in the prevention, treatment, control, amelioration, or reduction of risk of the diseases or conditions for which compounds of the present invention are useful. Such other drugs may be administered, by a route and in an amount commonly used therefore, contemporaneously or sequentially with a compound of the present invention. When a compound of the present invention is used contemporaneously with one or more other drugs, a pharmaceutical composition containing such other drugs in addition to the compound of the present invention is preferred. Accordingly, the pharmaceutical compositions of the present invention include those that also contain one or more other active ingredients, in addition to a compound of the present invention.

The weight ratio of the compound of the present invention to the other active ingredient(s) may be varied and will depend upon the effective dose of each ingredient. Generally, an effective dose of each will be used. Thus, for example, when a compound of the present invention is combined with another agent, the weight ratio of the compound of the present invention to the other agent will generally range from about 1000:1 to about 1:1000, or from about 200:1 to about 1:200. Combinations of a compound of the present invention and other active ingredients will generally also be within the aforementioned range, but in each case, an effective dose of each active ingredient should be used.

In such combinations the compound of the present invention and other active agents may be administered separately or in conjunction. In addition, the administration of one element may be prior to, concurrent to, or subsequent to the administration of other agent(s), and via the same or different routes of administration.

The compounds of the present invention may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, ICV, intracisternal injection or infusion, subcutaneous injection, or implant), by inhalation spray, nasal, vaginal, rectal, sublingual, or topical routes of administration and may be formulated, alone or together, in suitable dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles appropriate for each

route of administration. In addition to the treatment of warm-blooded animals the compounds of the invention are effective for use in humans.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active compound is included in an amount sufficient to produce the desired effect upon the process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, solutions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the techniques described in the U.S. Patents 4,256,108; 4,166,452; and 4,265,874 to form osmotic therapeutic tablets for control release. Oral tablets may also be formulated for immediate release, such as fast melt tablets or wafers, rapid dissolve tablets or fast dissolve films.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those

suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention are employed. Similarly, transdermal patches may also be used for topical administration.

The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions.

In the treatment, prevention, control, amelioration, or reduction of risk of conditions which require antagonism of CGRP receptor activity an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are may be provided in the form of tablets containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, or may be administered once or twice per day.

When treating, preventing, controlling, ameliorating, or reducing the risk of headache, migraine, cluster headache, or other diseases for which compounds of the present invention are indicated, generally satisfactory results are obtained when the compounds of the present invention are administered at a daily dosage of from about 0.1 milligram to about 100 milligram per kilogram of animal body weight, given as a single daily dose or in divided doses two to six times a day, or in sustained release form. For most large mammals, the total daily dosage is from about 1.0 milligrams to about 1000 milligrams, or

from about 1 milligrams to about 50 milligrams. In the case of a 70 kg adult human, the total daily dose will generally be from about 7 milligrams to about 350 milligrams. This dosage regimen may be adjusted to provide the optimal therapeutic response.

5 It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the host undergoing therapy.

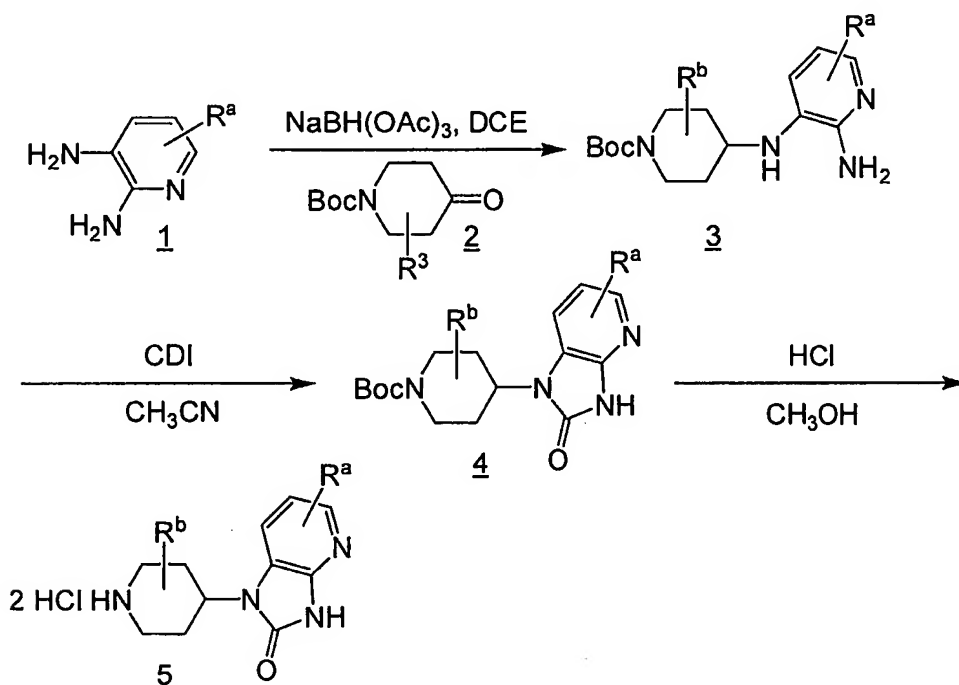
10 Several methods for preparing the compounds of this invention are illustrated in the following Schemes and Examples. Starting materials are made according to procedures known in the art or as illustrated herein.

The compounds of the present invention can be prepared readily according to the following Schemes and specific examples, or modifications thereof, using readily available starting materials, reagents and conventional synthesis procedures. In these reactions, it is also possible to make use of variants which are themselves known to those of ordinary skill in this art but are not mentioned in greater detail. The general procedures for making the compounds claimed in this invention can be readily understood and appreciated by one skilled in the art from viewing the following Schemes. The synthesis of intermediates and final compounds may be conducted as described in Schemes 1-7.

REACTION SCHEMES

Diamino heterocycles, such as 2,3-diaminopyridine 1, can be reductively alkylated with ketones such as 2 to give the monalkylated product 3 (Scheme 1). Ring closure with carbonyldiimidazole furnishes imidazolone 4. Final deprotection under standard conditions gives the intermediate 5.

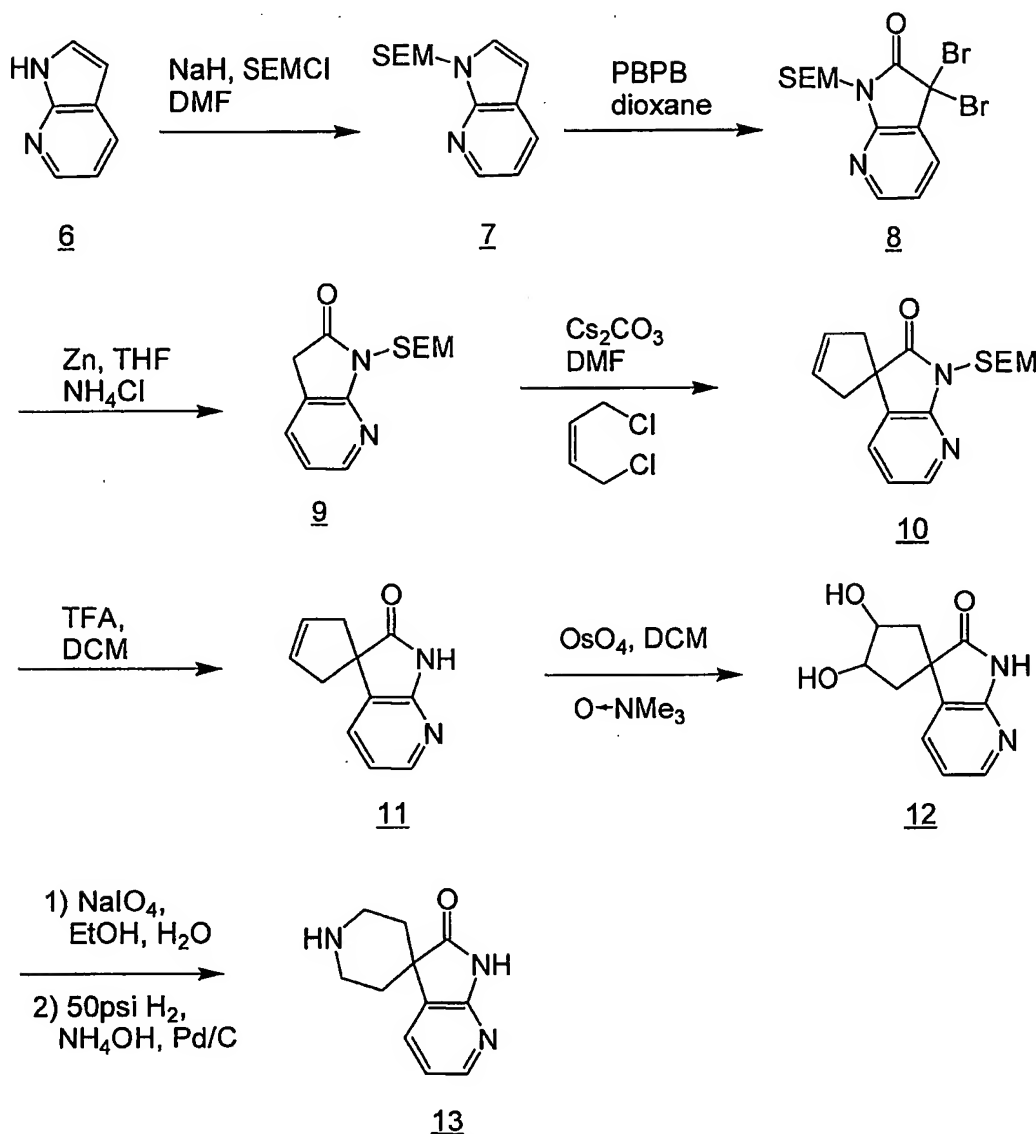
SCHEME 1



A representative synthesis of a spirolactam intermediate is shown in Scheme 2, using a spiroazaoxindole example. 7-Azaindole (6) may be protected with a variety of protecting groups, such as the (trimethylsilyl)ethoxymethyl group shown in Scheme 2. Following the method of Marfat and Carter (*Tetrahedron Lett.*, 1987, 28, 4027-4030), treatment of 7 with pyridine hydrobromide perbromide provides the dibromoazaoxindole 8, which may be reduced to the corresponding azaoxindole 9 by reaction with zinc. Alkylation of 9 with cis-1,4-dichloro-2-butene is carried out using cesium carbonate in DMF to afford the spiroazaoxindole 10. Removal of the SEM protecting group under standard conditions followed by osmium tetroxide catalyzed dihydroxylation provides the diol intermediate 12. Periodate oxidative cleavage of the diol, followed by a double reductive amination (*Org. Lett.*, 2000, 26, 4205-4208) affords the spiropiperidine 13. The methodology shown in Scheme 2 is not limited to

azaoxindoles such as 9, but may be applied to a variety of suitably protected heterocyclic systems to give the corresponding spiro compounds.

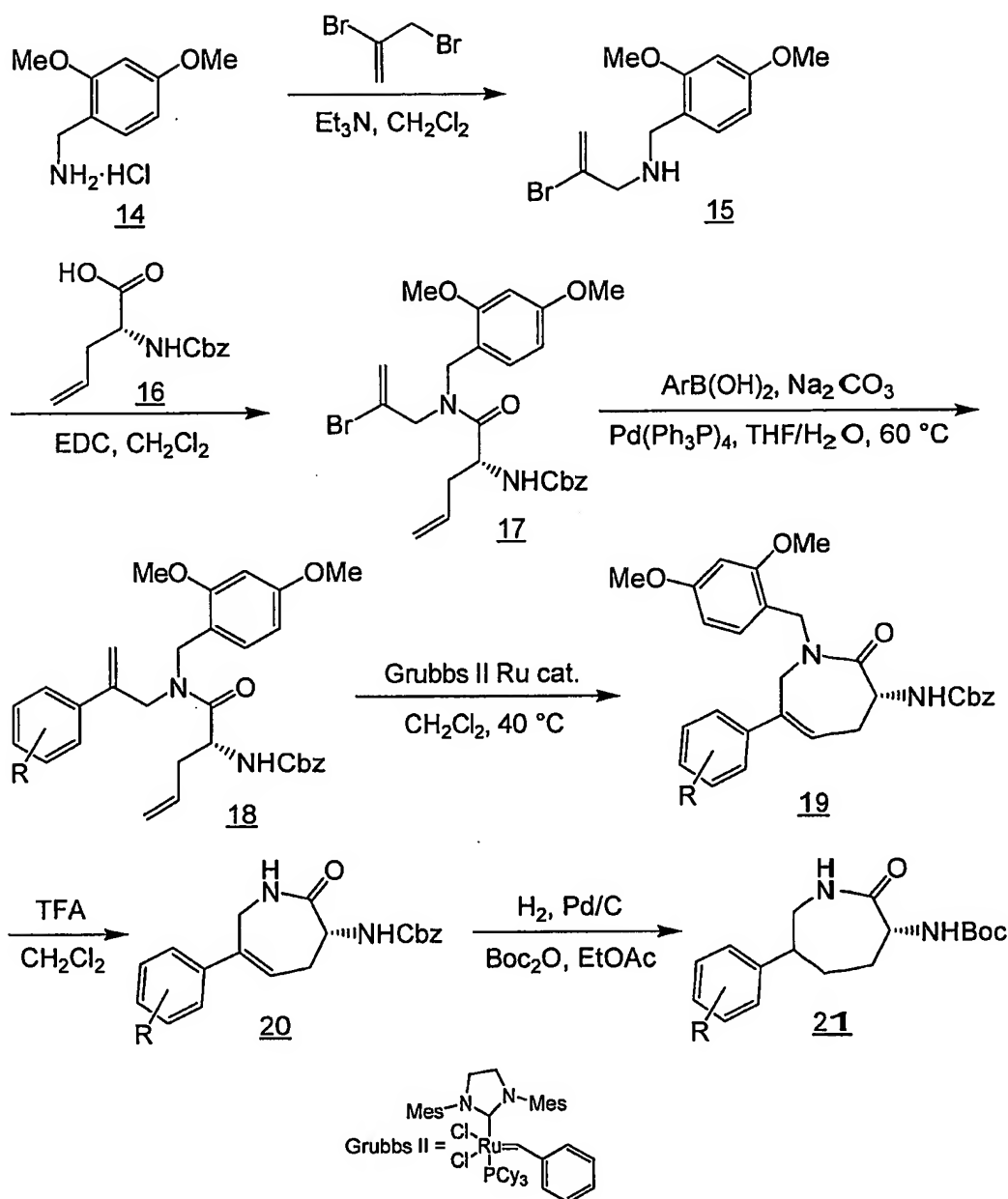
SCHEME 2



Caprolactams can be assembled following an olefin metathesis strategy as outlined in Scheme 3. 2,4-Dimethoxybenzylamine hydrochloride is alkylated with 2,3-dibromopropene under mild basic conditions to give amine 15. (2*R*)-2-[[[(benzyloxy)carbonyl]amino}pent-4-enoic acid (16), prepared in one step from commercially available D-allyl glycine according to known procedures (J. Chem. Soc., 1962, 3963-3968), can be coupled to amine 15 under a variety of conditions to give amide 17. A variety

of transition metal catalyzed cross couplings can be performed on the vinyl bromide, for example palladium-mediated arylations with phenylboronic acid and sodium carbonate, yielding styrene derivative 18. Ring-closing metathesis occurs in the presence of the Grubbs second generation ruthenium catalyst in dichloromethane with mild heating to afford lactam 19. Removal of the dimethoxybenzyl group and
5 hydrogenation with *in situ* protection of the primary amine gives the corresponding saturated lactam 21.

SCHEME 3



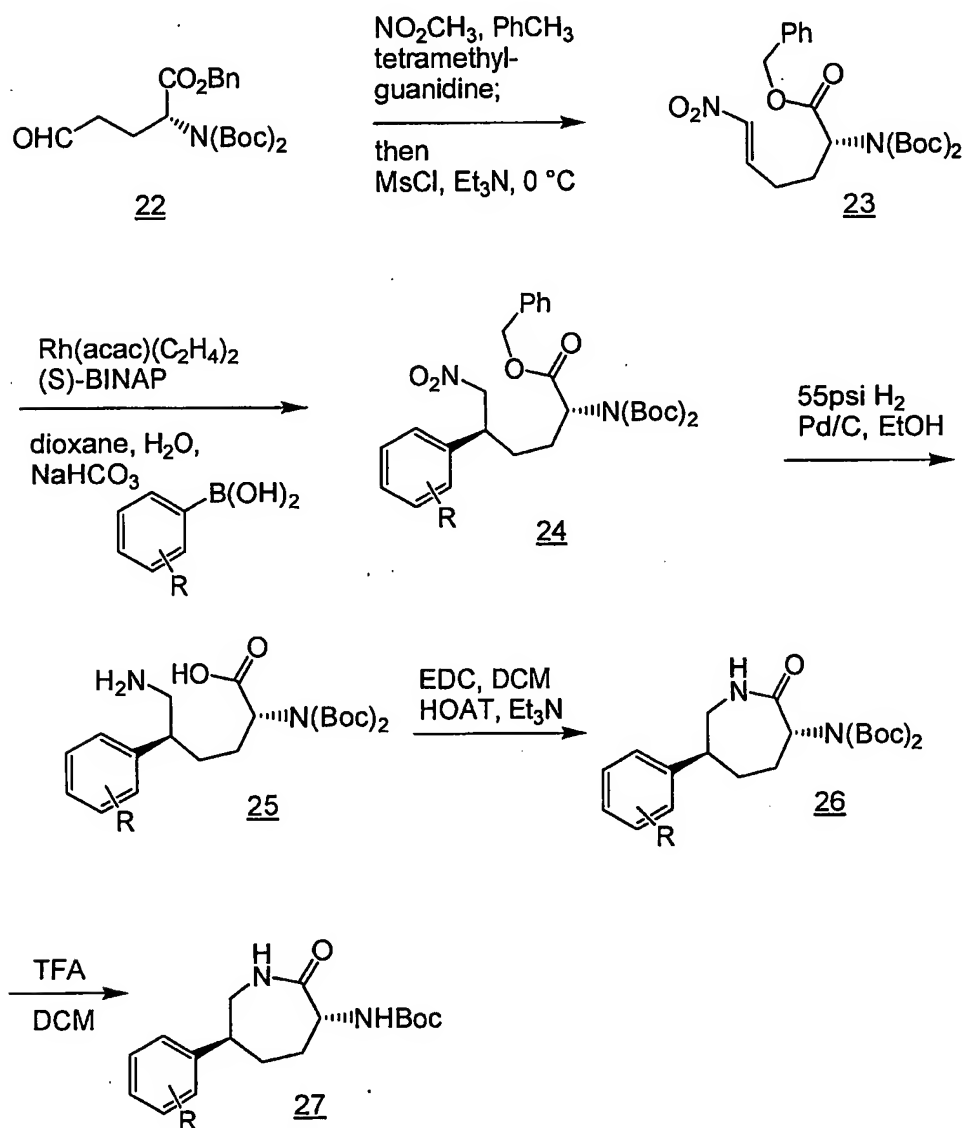
5

Alternatively, a C6-aryl group can be introduced as outlined in Scheme 4. Addition of nitromethane to the known glutamic acid derived aldehyde 22 (*Tetrahedron Asymmetry*, 1998, 3381-94), followed by *in situ* elimination affords nitro olefin 23. Addition of the aryl group via a boronic acid derivative, or similar equivalent, can be accomplished in a stereoselective manner through chiral ligand-

Rh catalysis. Concomitant nitro reduction and benzyl ester hydrogenolysis affords the amino acid 25. Ring closure under standard conditions, followed by removal of a single tert-butoxycarbonyl group furnishes the lactam 27.

5

SCHEME 4

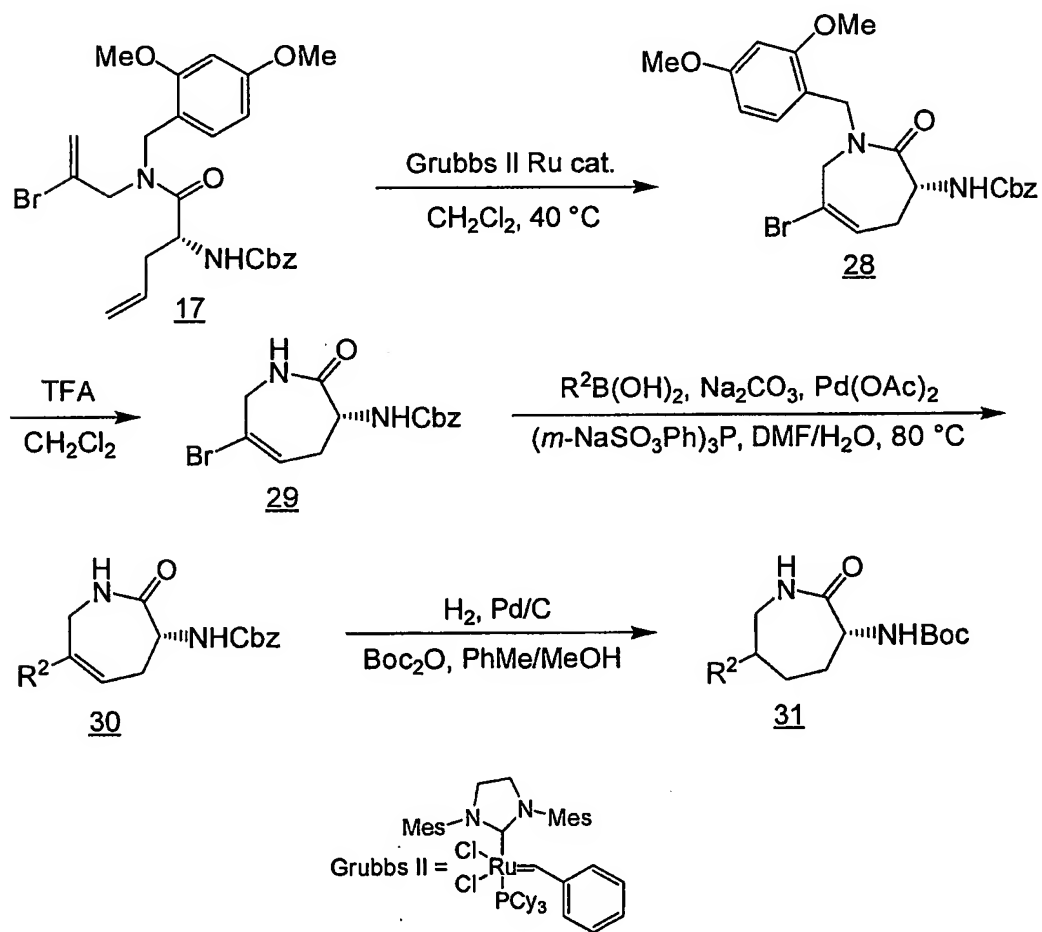


Variation at the 6-position of the caprolactams can be introduced by employing a similar strategy (Scheme 5). Ring-closing metathesis can be performed directly on vinyl bromide 17 using the Grubbs second generation ruthenium catalyst to give cyclic vinyl bromide 28. Removal of the dimethoxybenzyl group and palladium-mediated cross coupling, in this case with a boronic acid,

10

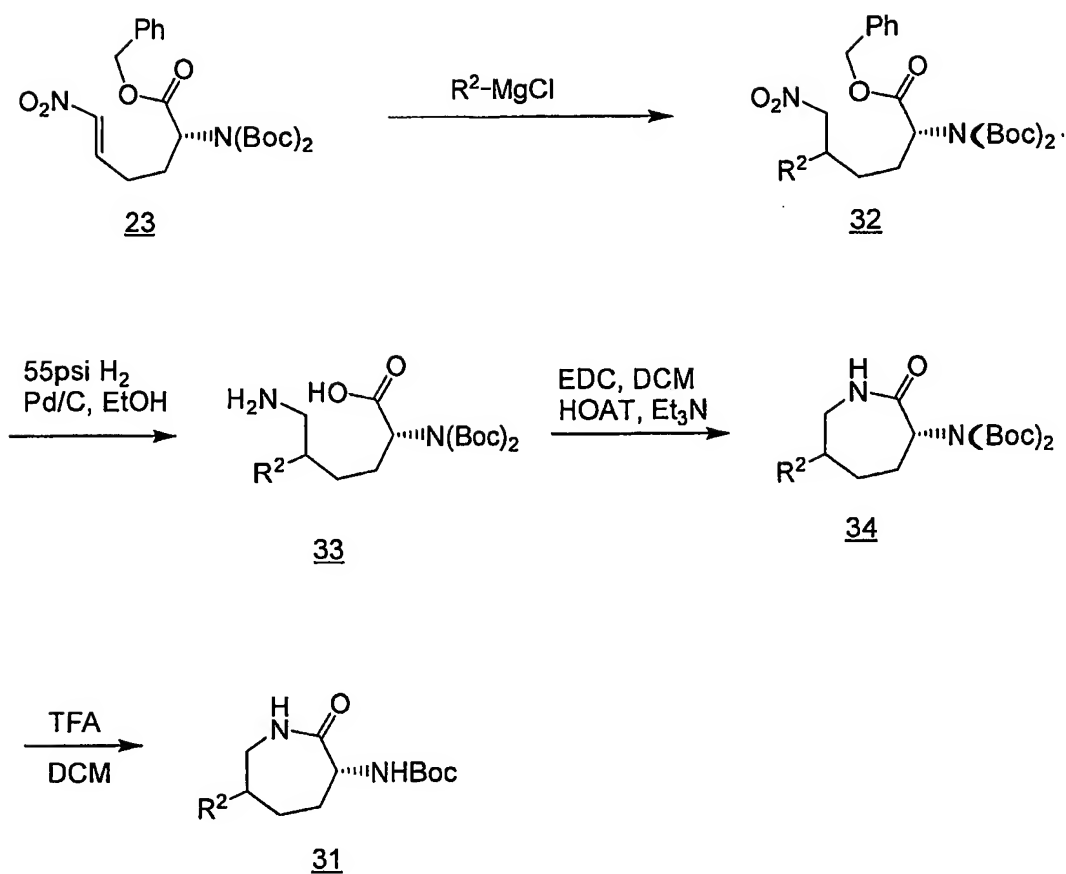
furnishes compounds of the general formula 30. The transformation of 29 to 30 is not limited to boronic acid derivatives. Standard hydrogenation yields compounds of the general formula 31.

SCHEME 5



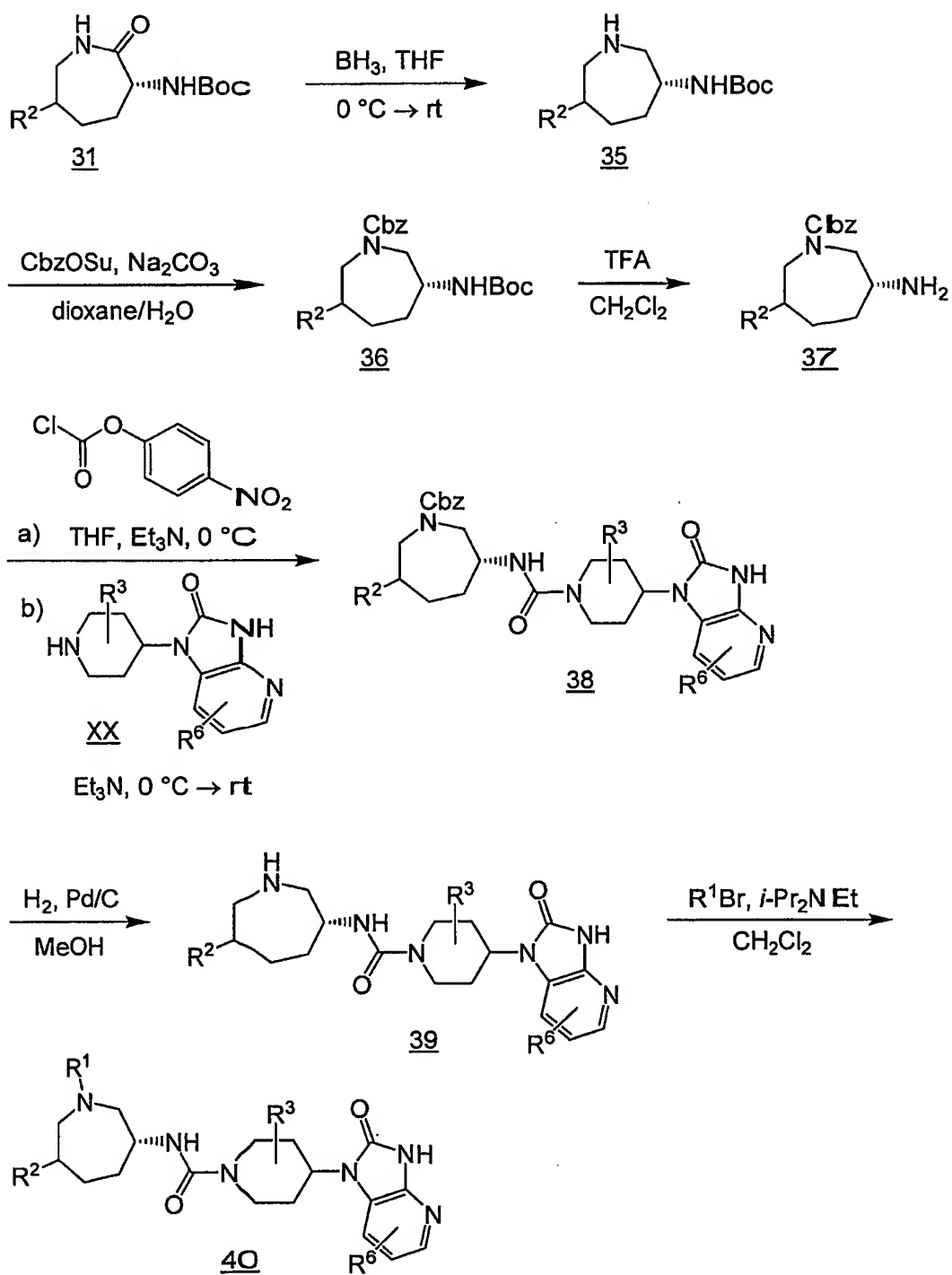
Alternatively, addition of a Grignard or similar reagent to the nitro olefin 23, followed by nitro reduction and benzyl ester hydrogenolysis affords various amino acids such as 33 (Scheme 6). Ring closure under standard conditions, followed by removal of a single tert-butoxycarbonyl group furnishes the lactam 31.

SCHEME 6



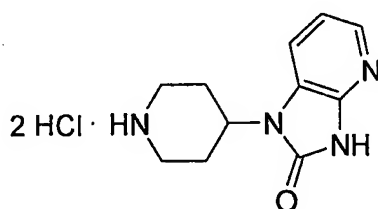
- 5 Azepane derivatives can be prepared as shown in scheme 7. Lactam intermediates are reduced with borane in tetrahydrofuran to yield the corresponding azepanes **35**. Protection of the secondary amine followed by deprotection of the primary amine with trifluoroacetic acid gives the coupling precursor **37**. This compound is reacted with 4-nitrophenyl chloroformate to form the reactive carbamate, then treated with the appropriate amine to provide urea **38**. Hydrogenolysis liberates the
- 10 secondary amine which can then be reacted with various alkyl and acyl halides to afford the substituted azepanes, such as **40**.

SCHEME 7



INTERMEDIATES AND EXAMPLES

The following examples are provided so that the invention might be more fully understood. These examples are illustrative only and should not be construed as limiting the invention in any way.

INTERMEDIATE 12-Oxo-1-(4-piperidiny)-2,3-dihydro-1H-imidazo[4,5-b]pyridine dihydrochlorideStep A. 2-Amino-3-[(1-*tert*-butoxycarbonylpiperidin-4-yl)amino]pyridine

Sodium triacetoxyborohydride (14.5 g, 68.7 mmol) was added to a solution of 2,3-diaminopyridine (5.00 g, 45.8 mmol) and *N*-(*tert*-butoxycarbonyl)-4-piperidone (9.58 g, 48.1 mmol) in dichloroethane (75 mL) at room temperature. After 5 h, additional sodium triacetoxyborohydride was added (1.8 g) and again after another 2.5 h. The reaction was stirred overnight, and quenched with 5% aqueous sodium hydroxide. This was extracted with methylene chloride, and washed with 5% aqueous sodium hydroxide, water and saturated sodium chloride solution. After drying over sodium sulfate, the solution was filtered and evaporated to give the crude product. This was purified by chromatography (silica gel, 3 to 5% methanol in methylene chloride gradient elution), which gave the title compound (4.44 g). MS 293 (M+1) ¹H NMR (500 MHz, CD₃OD) δ 7.32 (dd, *J* = 5, 1 Hz, 1H), 6.85 (dd, *J* = 8, 1 Hz, 1H), 6.59 (dd, *J* = 8, 5 Hz, 1H), 4.04 (d, *J* = 13 Hz, 2H), 3.46 (m, 1H), 2.98 (br s, 2H), 2.01 (dd, *J* = 12, 2 Hz, 2H), 1.46 (s, 9H), 1.37 (qd, *J* = 12, 4 Hz, 2H).

Step B. 2-Oxo-1-(1-*tert*-butoxycarbonylpiperidin-4-yl)-2,3-dihydro-1H-imidazo[4,5-b]pyridine

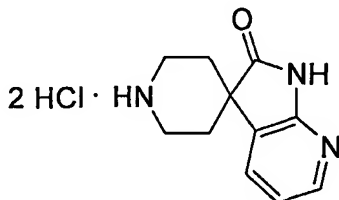
Carbonyldiimidazole (0.70 g, 4.33 mmol) was added to a solution of 2-amino-3-[(1-*tert*-butoxycarbonylpiperidin-4-yl)amino]pyridine (1.15 g, 3.93 mmol) in acetonitrile (150 mL) at room temperature. After several hours, an additional amount of carbonyldiimidazole was added (0.81 g), and the reaction stirred overnight. The acetonitrile was evaporated in vacuo, the residue partitioned between water and chloroform, and the organic phase washed with saturated brine and dried over magnesium

sulfate. The crude product was purified by chromatography (silica gel, 1.2 to 2.5% methanol in methylene chloride gradient elution), which gave the title compound (1.09 g). ¹H NMR (500 MHz, CDCl₃) δ 9.39 (br s, 1H), 8.04 (dd, *J* = 5, 1 Hz, 1H), 7.33 (dd, *J* = 8, 1 Hz, 1H), 6.99 (dd, *J* = 8, 5 Hz, 1H), 4.50 (m, 1H), 4.32 (br s, 2H), 2.86 (br s, 2H), 2.20 (m, 2H), 1.86 (d, *J* = 12 Hz, 2H), 1.50 (s, 9H).

Step C. 2-Oxo-1-(4-piperidinyl)-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridine dihydrochloride

2-Oxo-1-(1-*tert*-butoxycarbonylpiperidin-4-yl)-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridine (1.03 g, 3.23 mmol) was dissolved in methanol (25 mL) and a solution of 2 N hydrochloric acid in ether (8 mL) was added at room temperature. After 2 h, the volatiles were removed in vacuo, to give the title compound (0.92 g). MS 219 (*M* + 1). ¹H NMR (500 MHz, CD₃OD) δ 8.01 (dd, *J* = 6, 1 Hz, 1H), 7.83 (d, *J* = 8 Hz, 1H), 7.28 (dd, *J* = 8, 6 Hz, 1H), 4.60 (m, 1H), 3.59 (d, *J* = 12 Hz, 2H), 3.21 (t, *J* = 12 Hz, 2H), 2.70 (dq, *J* = 13, 4 Hz, 2H), 2.12 (d, *J* = 13 Hz, 2H).

INTERMEDIATE 2



Spiro[piperidine-4,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one dihydrochloride

Step A. 1-{[2-(Trimethylsilyl)ethoxy]methyl}-1*H*-pyrrolo[2,3-*b*]pyridine

Sodium hydride (60% dispersion in mineral oil; 16.2 g, 0.404 mmol) was added in portions over 25 min to a solution of 7-azaindole (39.8 g, 0.337 mol) in DMF (200 mL) at 0 °C and the mixture was stirred for 1 h. 2-(Trimethylsilyl)ethoxymethyl chloride (71.8 mL, 0.404 mmol) was then added slowly over 15 min, keeping the temperature of the reaction mixture below 10 °C. After 1 h, the reaction was quenched with H₂O (500 mL) and the mixture was extracted with CH₂Cl₂ (5 × 300 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered, concentrated and dried under high vacuum to give the title compound. MS: *m/z* = 249 (*M* + 1).

Step B. 3,3-Dibromo-1-{[2-(trimethylsilyl)ethoxy]methyl}-1,3-dihydro-2*H*-pyrrolo[2,3-*b*]pyridin-2-one

A solution of 1-{[2-(trimethylsilyl)ethoxy]methyl}-1*H*-pyrrolo[2,3-*b*]pyridine from Step A (43.1 g, 0.174 mol) in dioxane (300 mL) was added dropwise over 30 min to a suspension of pyridine

hydrobromide perbromide (277 g, 0.868 mol) in dioxane (300 mL). The reaction was stirred at ambient temperature using an overhead mechanical stirrer. After 60 min, the biphasic reaction mixture was quenched with H₂O (300 mL) and extracted with EtOAc. The aqueous layer was washed with EtOAc (2 × 300 mL) and the combined organic layers were washed with H₂O (4 × 300 mL; the final wash was pH 5-6), then brine (300 mL), then dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was immediately dissolved in CH₂Cl₂ and the solution filtered through a plug of silica, eluting with CH₂Cl₂ until the dark red color had completely eluted from the plug. The filtrate was washed with saturated aqueous NaHCO₃ (400 mL), then brine (400 mL), dried over MgSO₄ and concentrated *in vacuo* to give the title compound. MS: *m/z* = 423 (M + 1).

Step C. 1-([2-(Trimethylsilyl)ethoxy]methyl)-1,3-dihydro-2H-pyrrolo[2,3-*b*]pyridin-2-one

Zinc (100 g, 1.54 mol) was added to a solution of 3,3-dibromo-1-([2-(trimethylsilyl)ethoxy]methyl)-1,3-dihydro-2H-pyrrolo[2,3-*b*]pyridin-2-one from Step B (65 g, 0.154 mol) in THF (880 mL) and saturated aqueous ammonium chloride (220 mL). After 3 h, the reaction was filtered and concentrated *in vacuo*. The residue was partitioned between EtOAc and H₂O which resulted in the formation of a white precipitate. Both layers were filtered through a Celite pad and the layers were separated. The aqueous layer was washed with EtOAc (2 ×) and the combined organic layers were washed with H₂O, dried over MgSO₄, filtered, and concentrated. The crude product was filtered through a plug of silica gel eluting with CH₂Cl₂:EtOAc – 90:10 and the eluant was concentrated under reduced pressure to provide the title compound. MS: *m/z* = 265 (M + 1).

Step D. spiro[cyclopent-3-ene-1,3'-pyrrolo[2,3-*b*]pyridin]-2'(1'*H*)-one

To a solution of cis-1,4-dichloro-2-butene (1.98 g, 15.8 mmol) and 1-([2-(trimethylsilyl)ethoxy]methyl)-1,3-dihydro-2H-pyrrolo[2,3-*b*]pyridin-2-one (3.49 g, 13.2 mmol) in DMF (175 mL) was added cesium carbonate (10.7 g, 32.9 mmol). After 24 h the reaction mixture was partitioned between Et₂O (200 mL) and H₂O (200 mL). The aqueous layer was extracted further with Et₂O (2 × 200 mL). The combined organic layers were washed with H₂O (2 × 100 mL), then brine (100 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. To a solution of this material in dichloromethane (150 mL) was added trifluoroacetic acid (150 mL). After 1h, the reaction was concentrated, dissolved in EtOH (150 mL) and 2N HCl (150 mL) was added. This mixture was heated at 45 °C for 48 h. The mixture was concentrated, diluted with saturated aqueous NaHCO₃, and extracted with dichloromethane (2x). The combined organic layers were dried and concentrated. The crude product was purified by silica gel chromatography, eluting with a gradient of 0 to 5% methanol : dichloromethane to give the title compound (0.62 g). MS: *m/z* = 187.1 (M + 1).

Step E. 3,4-dihydroxySpiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'-(1'*H*)-one

To a mixture of trimethylamine-N-oxide dihydrate (408 mg, 3.67 mmol) and spiro[cyclopent-3-ene-1,3'-pyrrolo[2,3-*b*]pyridin]-2'-(1'*H*)-one (622 mg, 3.34 mmol) in dichloromethane (115 mL) was added osmium tetroxide (25 μ L of 2.5% solution in 2-methyl-2-propanol). After 24 h the reaction mixture was concentrated. The crude product was loaded onto a silica gel chromatography column with a minimal amount of methanol and eluted with a gradient of 5 to 20% methanol : dichloromethane to give the title compound (0.63 g). MS: m/z = 221.0 ($M + 1$).

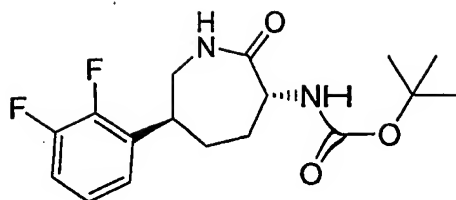
Step F. *tert*-butyl 2'-oxo-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*b*]pyridine]-1-carboxylate

To a mixture of 3,4-dihydroxySpiro[cyclopentane-1,3'-pyrrolo[2,3-*b*]pyridin]-2'-(1'*H*)-one (640 mg, 2.91 mmol) in 3 : 1 ethanol : water (160 mL) was added sodium periodate (622 mg, 2.91 mmol). Upon consumption of the starting material, ammonium hydroxide (50 mL) was slowly added to the reaction mixture. Palladium hydroxide (200 mg, 20%) was added and the reaction was hydrogenated at 50 psi. After 24 h, 200 mg of palladium hydroxide was added and the hydrogenation continued for an additional 24 h. The reaction mixture was filtered through celite and concentrated. This material was dissolved in DMF (10 mL) and di-*tert*-butyl dicarbonate (635 mg, 2.91 mmol) was added followed by triethylamine (0.811 mL, 5.82 mmol). After 24 h, the reaction was diluted with saturated aqueous NaHCO₃ and extracted with ether (3x). The combined organic layers were washed with water (3x), dried and concentrated. The crude product was purified by silica gel chromatography, eluting with a gradient of 0 to 10% methanol : dichloromethane to give the title compound (489 mg). MS: m/z = 304.1 ($M + 1$).

Step G. Spiro[piperidine-4,3'-pyrrolo[2,3-*b*]pyridin]-2'-(1'*H*)-one dihydrochloride

tert-Butyl 2'-oxo-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*b*]pyridine]-1-carboxylate (451 mg, 1.49 mmol) was dissolved in ethyl acetate (3 mL) and a solution of 4N hydrochloric acid in dioxane (7.5 mmol) was added at room temperature. After 24 h, the volatiles were removed in vacuo, to give the title compound (404 mg). MS 204.1 ($M + 1$). ¹H NMR (500 MHz, CD₃OD) δ 8.31 (d, J =7.1 Hz, 1H), 8.20 (d, J =6.1 Hz, 1H), 7.45 (dd, J =6.8, 6.8 Hz, 1H), 3.74 (brdd, 2H), 3.47 (brdd, 2H), 2.35 (brddd, 2H), 2.21 (brd, 2H).

INTERMEDIATE 3



tert-Butyl (3R,6S)-6-(2,3-difluorophenyl)-2-oxoazepan-3-ylcarbamate

Step A. 2-Bromo-N-(2,4-dimethoxybenzyl)prop-2-en-1-amine

5 Triethylamine (16.0 mL, 114 mmol) was added to a solution of 2,4-dimethoxybenzylamine hydrochloride (11.1 g, 54.5 mmol) and 2,3-dibromopropene (10.9 g, 54.5 mmol) in dichloromethane (200 mL). After 18 h, water was added and the mixture was extracted with dichloromethane (3x). The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography [100%
10 dichloromethane → 95% dichloromethane/ 5% (10% ammonium hydroxide/ methanol)] gave the title compound (7.85 g).

Step B. Benzyl (1R)-1-{[(2-bromoprop-2-enyl)(2,4-dimethoxybenzyl) amino]carbonyl}but-3-enylcarbamate

15 1-[3-(Dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (55 mg, 0.285 mmol) was added to a solution of 2-bromo-N-(2,4-dimethoxybenzyl)prop-2-en-1-amine (73 mg, 0.256 mmol) and (2R)-2-{[(benzyloxy)carbonyl]amino}pent-4-enoic acid (71 mg, 0.285 mmol) in dichloromethane (5 mL). After 18 h the mixture was concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 30% ethyl acetate/ hexanes) gave the title compound (77 mg). MS 517 (M+1).

20

Step C. Benzyl (1R)-1-{[[2-(2,3-difluorophenyl)prop-2-enyl](2,4-dimethoxybenzyl)amino]carbonyl}but-3-enylcarbamate

Dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium dichloromethane adduct (0.726 g, 0.889 mmol) was added to a solution of benzyl (1R)-1-{[(2-bromoprop-2-enyl)(2,4-dimethoxybenzyl)amino]carbonyl}but-3-enylcarbamate (9.2 g, 17.8 mmol), 2,3-difluorophenylboronic acid (2.95 g, 18.7 mmol) and sodium carbonate (2M in water; 19.6 mL, 39.1 mmol) in *N,N*-dimethylformamide (60 mL) and the mixture was heated to 75 °C. After 2 h, the mixture was allowed to cool to ambient temperature and extracted with dichloromethane (3x). The combined organic extracts were washed with saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 55% ethyl acetate/ hexanes) gave the title compound (6.8 g). MS 551.2 (M+1).

Step D. Benzyl (3R)-6-(2,3-difluorophenyl)-1-(2,4-dimethoxybenzyl)-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-ylcarbamate

[1,3-bis-(2,4,6-Trimethylphenyl-2-imidazolidinylidene)dichloro(phenylmethylene)-(tricyclohexylphosphine)ruthenium] (Grubbs second generation catalyst) (2.62 g, 3.09 mmol) was added to a solution of benzyl (1R)-1-{[[2-(2,3-difluorophenyl)prop-2-enyl](2,4-dimethoxybenzyl)amino]carbonyl}but-3-enylcarbamate (6.8 g, 12.35 mmol) in dichloromethane (1800 mL) and the solution was heated to 40°C. After 48 h, additional catalyst was added (0.52 g, 0.61 mmol) and the reaction continued to heat at 40 °C for an additional 48 h. The mixture was allowed to cool to ambient temperature and concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 55% ethyl acetate/ hexanes) gave the title compound (3.71 g). MS 523.1 (M+1).

Step E. Benzyl (3R)-6-(2,3-difluorophenyl)-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-ylcarbamate

Trifluoroacetic acid (60 mL) was added to a solution of benzyl (3R)-6-(2,3-difluorophenyl)-1-(2,4-dimethoxybenzyl)-2-oxo-2,3,4,7-tetrahydro-1H-azepin-3-ylcarbamate (3.70 g, 7.08 mmol) in dichloromethane (40 mL). After 18 h, the mixture was concentrated at 25 °C, methanol (150 mL) was added, and the precipitate filtered. The filtrate was concentrated, diluted with dichloromethane (100 mL), washed with water (2x), saturated aqueous sodium bicarbonate (2x), saturated brine, dried over magnesium sulfate, filtered and concentrated. Purification by silica gel chromatography (5% ethyl acetate/ hexanes → 65% ethyl acetate/ hexanes) gave the title compound (1.75 g). MS 373.1 (M+1).

Step F. *tert*-Butyl (3*R*,6*S*)-6-(2,3-difluorophenyl)-2-oxoazepan-3-ylcarbamate

10% Palladium on carbon (700 mg) was added to a solution of benzyl (3*R*)-6-(2,3-difluorophenyl)-2-oxo-2,3,4,7-tetrahydro-1*H*-azepin-3-ylcarbamate (2.6 g, 6.98 mmol) and di-*tert*-butyl dicarbonate (5.03 g, 23.0 mmol) in toluene (200 mL). The reaction vessel was evacuated and back-filled with nitrogen (3x), then back-filled with hydrogen (1 atm). After 24 h, the mixture was filtered and concentrated. Purification by preparative reverse phase chromatography (DeltaPak C18, 15 μ , 47 mm x 300 mm, 70 mL/min : 80% H₂O/NH₄OAc : 20% CH₃CN to 100% CH₃CN over 60 min) afforded the pure trans title compound (1.2 g) as well as the pure cis compound. MS 341.2 (M+1). ¹H NMR (trans) (500 MHz, CDCl₃) δ 7.07-7.04 (m, 2H), 6.91-6.89 (m, 1H), 6.04 (br s, 1H), 5.93 (d, *J* = 5.6 Hz, 1H), 4.46 (dd, *J* = 10.5, 4.6 Hz, 1H), 3.65-3.59 (m, 1H), 3.21 (dd, *J* = 15.1, 7.3 Hz, 1H), 3.05-3.00 (m, 1H), 2.25-2.20 (m, 1H), 2.17-2.10 (m, 2H), 1.79-1.71 (m, 1H), 1.46 (s, 9H).

Alternatively, Intermediate 3 can be made in the following manner:

Step G. 1-Benzyl 5-methyl *N,N*-bis(*tert*-butoxycarbonyl)-D-glutamate

To a solution of Boc-D-Glu-OBn (50.0 g, 148.2 mmol) in DCM (400 ml) and MeOH (100 ml) was added trimethylsilyldiazomethane (88.9 mL of 2.0 M solution in hexanes, 117.8 mmol) at 0 °C dropwise via an addition funnel. After 60 min the reaction was concentrated. This residue was diluted with CH₃CN (400 mL) and (Boc)₂O (48.5 g, 222.3 mmol) was added followed by DMAP (18.1 g, 14.8 mmol). After 24 h the reaction was concentrated and purified by silica gel chromatography (10% → 60% ethyl acetate/ hexanes) to give the title compound (48.20 g, 72%). MS 252.2 (M+1 – 2Boc).

Step H. Benzyl (2*R*,5*E*)-2-[bis(*tert*-butoxycarbonyl)amino]-6-nitrohex-5-enoate

To a -78 °C of 1-benzyl 5-methyl *N,N*-bis(*tert*-butoxycarbonyl)-D-glutamate (48.2 g, 106.8 mmol) in Et₂O (400 mL), was added DIBAL (133.4 mL of 1.0 M solution in toluene, 133.4 mmol) slowly so as not to let the internal temperature exceed -65 °C. After 15 min, 20 mL more of DIBAL was added. After stirring for additional 20 min, water (300 mL) was added and the reaction was warmed to room temperature and stirred for 30 min. This mixture was further diluted with Et₂O and H₂O, the layers separated and the aqueous phase extracted with more Et₂O. The combined organics extracts were washed with a saturated aqueous solution of sodium potassium tartrate (2x), brine, dried over magnesium sulfate, filtered and concentrated to give benzyl *N,N*-bis(*tert*-butoxycarbonyl)-5-oxo-D-norvalinate (44.4 g) which was carried directly into the next step. MS 444.1 (M+Na). This material was dissolved in toluene (310 mL) and nitromethane (57.1 mL, 1.05 mol) and 1,1,3,3-tetramethylguanidine (1.3 mL, 10.5 mmol) were added at 0 °C. After stirring for 30 min the nitroaldol reaction was complete, so methanesulfonyl chloride (12.2 mL, 158 mmol) was added followed triethylamine (22.0 mL, 158 mmol) at 0 °C and the reaction was allowed to warm to RT. After 1 h, 4 mL MsCl and 5.5 mL triethylamine were added. After stirring

for an additional 30 min the mixture was diluted with Et₂O and NaHCO₃, the phases separated and the aqueous layer backwashed with another portion of Et₂O. The combined organics were dried over magnesium sulfate, filtered and concentrated to give a residue that was purified by silica gel chromatography (5% → 50% ethyl acetate/ hexanes) to give the title compound (34.3 g, 70%). MS 487.1 (M+Na).

Step I. Benzyl (5S)-N,N-bis(tert-butoxycarbonyl)-5-(2,3-difluorophenyl)-6-nitro-D-norleucinate

A solution of benzyl (2R,5E)-2-[bis(tert-butoxycarbonyl)amino]-6-nitrohex-5-enoate (34.0 g, 73.2 mmol), 2,3-difluorophenylboronic acid (28.9 g, 183.0 mmol) and water (4.62 mL, 256.2 mmol) in dioxane (240 mL) was degassed with argon for 15 min. To this solution was added sodium bicarbonate (3.08 g, 36.6 mmol), (S)-BINAP (1.28 g, 2.05 mmol) and acetylacetonobis(ethylene)rhodium(I) (0.472 g, 1.83 mmol). The mixture was stirred at RT for 2 min then heated to 35 °C. After 4 h, 255 mg of (S)-BINAP and 94 mg of acetylacetonobis(ethylene)rhodium(I) were added. After an additional 2 h the reaction was diluted with DCM/NaHCO₃, the layers separated and the aqueous phase was backwashed with another portion of DCM. The combined organics were dried over magnesium sulfate, filtered and concentrated to give a residue that was purified by silica gel chromatography (5% → 60% ethyl acetate/ hexanes) to give the title compound (37.0 g, 87%) contaminated with ~5% 5R isomer. MS 379.1 (M+1 – 2Boc).

Step J. (5S)-N²,N²-Bis(tert-butoxycarbonyl)-5-(2,3-difluorophenyl)-D-lysine

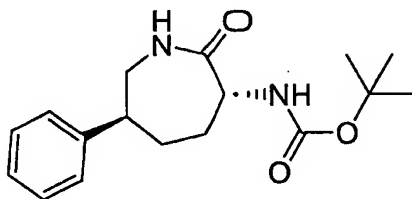
A solution of benzyl (5S)-N,N-bis(tert-butoxycarbonyl)-5-(2,3-difluorophenyl)-6-nitro-D-norleucinate (15.5 g, 26.8 mmol) and 10% Pd/C (12.0 g) in EtOH (175 mL, SureSeal from Aldrich), was hydrogenated at 55 psi overnight. After 18 h, another 4 g of 10% Pd/C was added and the reaction hydrogenated at 55 psi for another 18 h. The reaction was filtered through Celite with more EtOH and concentrated to afford the title compound (12.0 g). MS 459.2 (M+1).

Step K. tert-Butyl (3R,6S)-6-(2,3-difluorophenyl)-2-oxoazepan-3-ylcarbamate

To a solution (5S)-N²,N²-bis(tert-butoxycarbonyl)-5-(2,3-difluorophenyl)-D-lysine (22.0 g, 48.0 mmol) in DCM (700 mL) were added EDC (11.0 g, 57.6 mmol) and HOAT (3.27 g, 24.0 mmol) followed by triethylamine (10.0 mL, 72.0 mmol). After 60 min, NaHCO₃ was added, the layers separated and the aqueous phase backwashed with DCM. The combined organics were dried over magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (10% MeOH / DCM) to give the cyclized compound (18.0 g). A portion of this material (2.60 g, 5.90 mmol) was diluted DCM (60 mL) and TFA (1.20 mL, 11.8 mmol) was added. After 1 h, NaHCO₃ was added, the layers separated and the aqueous phase backwashed with DCM. The combined organics were dried over

magnesium sulfate, filtered and concentrated and the residue purified by silica gel chromatography (5% → 50% EtOAc / DCM) to give the title compound (1.14 g). MS 341.1 (M+1).

INTERMEDIATE 4

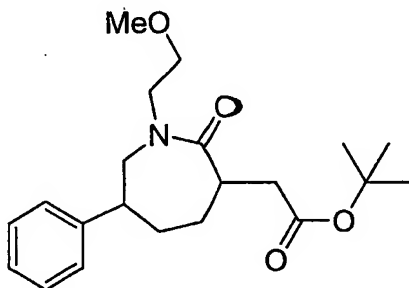


tert-Butyl (3R,6S)-6-phenyl-2-oxoazepan-3-ylcarbamate

The title compound was prepared using a similar procedure to Intermediate 3. MS 305.2

(M+1).

INTERMEDIATE 5



tert-Butyl[1-(2-methoxyethyl)-2-oxo-6-phenylazepan-3-yl]acetate

Step A. 1-(2-Methoxyethyl)-6-phenylazepan-2-one

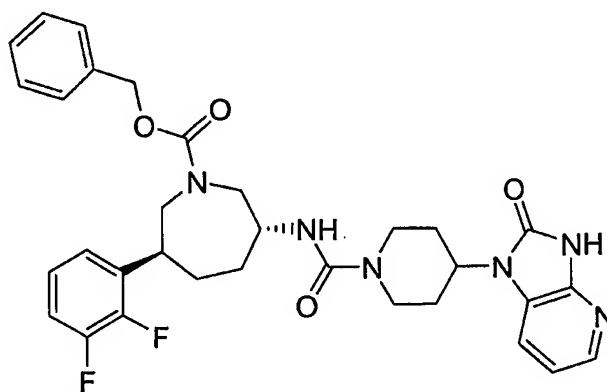
Sodium hydride (60% dispersion in mineral oil; 0.32 g, 8.03 mmol) was added to a solution of 6-phenylazepan-2-one (*J. Med. Chem.*, **1988**, 31, 422-428) (0.76 g, 4.02 mmol) in *N,N*-dimethylformamide (15 mL) at 0 °C, followed by the addition of 2-bromoethyl methyl ether (0.837 g, 6.03 mmol), and the mixture was allowed to warm to ambient temperature. After 21 h, water was added and the mixture was extracted with ethyl acetate (3x). The combined organic extracts were washed with water (3x), saturated brine, dried over sodium sulfate, filtered and concentrated. MS 248.3 (M+1).

Step B. tert-Butyl[1-(2-methoxyethyl)-2-oxo-6-phenylazepan-3-yl]acetate

Lithium diisopropylamide (1.8 M in heptane/tetrahydrofuran/ethylbenzene; 0.58 g, 5.41 mmol) was added to a solution of 1-(2-methoxyethyl)-6-phenylazepan-2-one (1.03 g, 4.16 mmol) in tetrahydrofuran (40 mL) at -78°C . After 2 h, *tert*-butylbromoacetate was added. After an additional 1.5 h, the reaction was quenched with methanol and allowed to warm to ambient temperature and

5 concentrated. Purification by reverse phase HPLC (C-18, 95% water/ acetonitrile \rightarrow 5% water/ acetonitrile with 0.1% trifluoroacetic acid) gave 450 mg (cis isomer) and 350 mg (trans isomer) of the title compound. MS 362 (M+1). cis isomer: ^1H NMR (500 MHz, CDCl_3) δ 7.29 (t, $J = 7.6$ Hz, 2H), 7.26 (m, 1H), 7.22-7.20 (m, 2H), 4.04 (br d, $J = 15.2$ Hz, 1H), 3.84 (dt, $J = 13.9, 4.9$ Hz, 1H), 3.51 (dd, $J = 15.4, 3.9$ Hz, 1H), 3.40-3.35 (m, 1H), 3.30-3.21 (m, 2H), 3.24 (s, 3H), 3.02-3.00 (m, 1H), 2.84 (dd, $J =$
10 16.4, 7.6 Hz, 1H), 2.68-2.66 (m, 1H), 2.33 (dd, $J = 16.4, 6.8$ Hz, 1H), 2.11-2.07 (m, 1H), 2.05-1.95 (m, 1H), 1.80-1.76 (m, 2H), 1.46 (s, 9H). trans isomer: ^1H NMR (500 MHz, CDCl_3) δ 7.32 (t, $J = 7.3$ Hz, 2H), 7.24-7.21 (m, 1H), 7.18 (d, $J = 7.1$ Hz, 2H), 3.96 (dd, $J = 14.9, 10.0$ Hz, 1H), 3.82-3.77 (m, 1H), 3.56-3.46 (m, 2H), 3.43-3.38 (m, 1H), 3.34 (s, 3H), 3.30 (d, $J = 15.1$ Hz, 1H), 3.20-3.15 (m, 1H), 2.85 (dd, $J = 16.6, 7.8$ Hz, 1H), 2.78 (br t, 1H), 2.26 (dd, $J = 16.6, 6.6$ Hz, 1H), 2.10 (br d, $J = 22.7, 9.3$ Hz,
15 1H), 1.77-1.73 (m, 1H), 1.62-1.59 (m, 1H), 1.46 (s, 9H).

EXAMPLE 1



20 Benzyl (3S,6R)-3-(2,3-difluorophenyl)-6-({[4-(2-oxo-2,3-dihydro-1H-imidazo[4,5-b]pyridin-1-yl)piperidin-1-yl]carbonyl}amino)azepan-1-carboxylate

Step A. *tert*-Butyl(3R,6S)-6-(2,3-difluorophenyl)azepan-3-ylcarbamate

25 Borane-THF (1.0 M in THF; 5.87 mL, 5.87 mmol) was added to a solution of *tert*-butyl[(3R,6S)-6-(2,3-difluorophenyl)-2-oxoazepan-3-yl]carbamate (1.0 g, 2.94 mmol) in tetrahydrofuran (100 mL). After 30 minutes, the reaction was quenched with methanol, followed by saturated sodium bicarbonate. The mixture was extracted with ethyl acetate (3x), and the combined organic extracts were

washed with water, saturated brine, dried over sodium sulfate, filtered and concentrated. MS 327.1 (M+1).

Step B. Benzyl(3*R*,6*S*)-3-[(*tert*-butoxycarbonyl)amino]-6-(2,3-difluorophenyl) azepane-1-carboxylate

5 *N*-(Benzyloxycarbonyloxy)succinimide (769 mg, 3.08 mmol) was added to a solution of *tert*-butyl(3*R*,6*S*)-6-(2,3-difluorophenyl)azepan-3-ylcarbamate (959 mg, 2.94 mmol) and sodium carbonate (311 mg, 2.94 mmol) in dioxane (20 mL) and water (10 mL). After 1.5 h, water was added. The reaction mixture was extracted with ethyl acetate (3x), and the combined organic extracts were washed with water, saturated brine, dried over sodium sulfate, filtered and concentrated.

10 Purification by silica gel chromatography (100% hexanes → 60% ethyl acetate/ hexanes) gave the title compound (0.92 g). MS 461.0 (M+1).

Step C. Benzyl(3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl) azepane-1-carboxylate

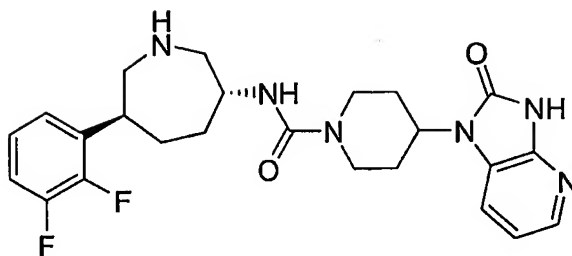
15 Trifluoroacetic acid (3 mL) was added to a solution of benzyl(3*R*,6*S*)-3-[(*tert*-butoxycarbonyl)amino]-6-(2,3-difluorophenyl) azepane-1-carboxylate (300 mg, 0.651 mmol) in dichloromethane (3 mL). After 1 h, saturated sodium bicarbonate was added. The mixture was extracted with dichloromethane (3x), and the combined organic extracts were washed with saturated brine, dried over sodium sulfate, filtered and concentrated. MS 361 (M+1). ¹H NMR (500 MHz, CDCl₃) δ 7.49-7.31 (m, 5 H), 7.07-6.99 (m, 3H), 6.89-6.87 (m, 1H), 5.23-5.12 (m, 2H), 3.87-3.73 (m, 1H), 3.69-3.58 (m, 1H),

20 3.55-3.50 (m, 1H), 3.32-3.20 (m, 2H), 3.12-3.11 (m, 1H), 2.11-2.05 (m, 1H), 1.94-1.89 (m, 1H), 1.82-1.75 (m, 1H).

Step D. Benzyl (3*S*,6*R*)-3-(2,3-difluorophenyl)-6-({[4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidin-1-yl]carbonyl}amino)azepane-1-carboxylate

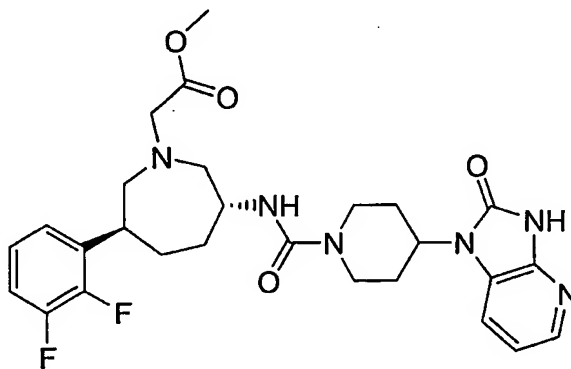
25 Triethylamine (91 μL, 0.651 mmol) was added to a solution of benzyl(3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl) azepane-1-carboxylate (235 mg, 0.651 mmol) and 4-nitrophenyl chloroformate (131 mg, 0.651 mmol) in tetrahydrofuran (5 mL) at 0 °C. After 1 h, 2-oxo-1-piperidinium-4-yl-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-4-ium dichloride (190 mg, 0.651 mmol) and triethylamine (0.273 mL, 1.953 mmol) were added and the mixture allowed to warm to ambient temperature. After 18 h, saturated

30 aqueous sodium carbonate was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate (3x), saturated brine, dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography [100% dichloromethane → 95% dichloromethane/ 5% (10% ammonium hydroxide/ methanol)] gave the title compound (0.240 g). MS 605.2655 (M+1).

EXAMPLE 2

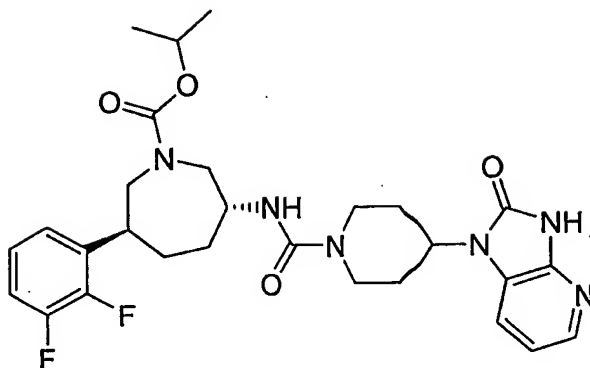
5 *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide

10 10% palladium on carbon (48 mg) was added to a solution of benzyl (3*S*,6*R*)-3-(2,3-difluorophenyl)-6-({[4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidin-1-yl]carbonyl}amino)azepane-1-carboxylate (240 mg, 0.397 mmol) in methanol (6 mL). The reaction vessel was evacuated and back-filled with nitrogen (3x), then back-filled with hydrogen (1 atm). After 2 h, the reaction was filtered and concentrated. MS 471.2291 (*M*+1).

EXAMPLE 3

15 Methyl [(3*S*,6*R*)-3-(2,3-difluorophenyl)-6-({[4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidin-1-yl]carbonyl}amino)azepan-1-yl]acetate

20 Methyl bromoacetate (13 μ L, 0.138 mmol) was added to a solution of *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (50.0 mg, 0.106 mmol) and diisopropylethylamine (19 μ L, 0.106 mmol) in dichloromethane (3 mL). After 18 h, the mixture was concentrated. Purification by silica gel chromatography [100% dichloromethane \rightarrow 95% dichloromethane/ 5% (10% ammonium hydroxide/ methanol)] gave the title compound (45 mg). MS 543.2526 (*M*+1).

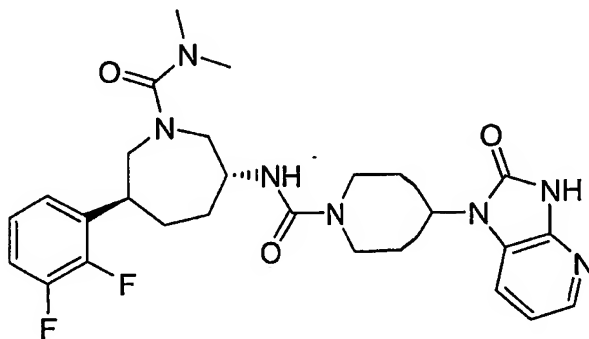
EXAMPLE 4

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Isopropyl (3*S*,6*R*)-3-(2,3-difluorophenyl)-6-((4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidin-1-yl)carbonyl)azepane-1-carboxylate

Isopropyl chloroformate (1.0 M in toluene; 43 μ L, 0.043 mmol) was added to a solution of *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (20.0 mg, 0.043 mmol) and diisopropylethylamine (7 μ L, 0.043 mmol) in dichloromethane (1 mL) at 0 °C. After 2 h, water was added. The mixture was extracted with dichloromethane (3x), and the combined organic extracts were washed with water, saturated brine, dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography [100% dichloromethane \rightarrow 95% dichloromethane/ 5% (10% ammonium hydroxide/ methanol)] gave the title compound (16.9 mg). MS 557.2657 (*M*+1).

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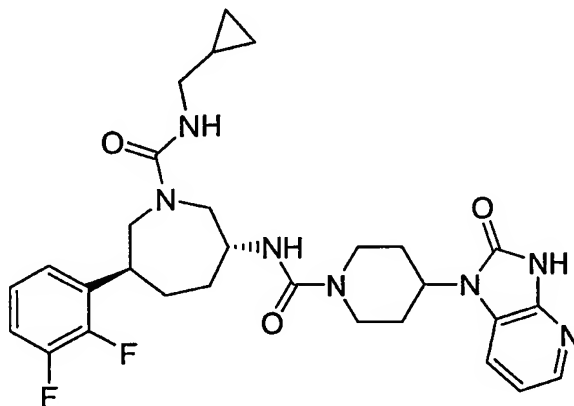
EXAMPLE 5

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(3*S*,6*R*)-3-(2,3-difluorophenyl)-*N,N*-dimethyl-6-((4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidin-1-yl)carbonyl)azepane-1-carboxamide

N,N-Dimethylcarbamoyl chloride (4 μ L, 0.043 mmol) was added to a solution of *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (20.0 mg, 0.043 mmol) and diisopropylethylamine (7 μ L, 0.043 mmol) in dichloromethane (1 mL). After 18 h, the mixture was concentrated. Purification by silica gel chromatography [100% dichloromethane \rightarrow 95% dichloromethane/ 5% (10% ammonium hydroxide/ methanol)] gave the title compound (19.7 mg). MS 542.2693 (*M*+1). The title compound was converted to the HCl salt with 2M HCl in ether. ^1H NMR (500 MHz, CD_3OD) δ 8.06 (d, *J* = 7.8 Hz, 1H), 8.01 (d, *J* = 6.1 Hz, 1H), 7.43 (dd, *J* = 7.8, 6.4 Hz, 1H), 7.15-7.14 (m, 3H), 4.56-4.51 (m, 1H), 4.25 (br s, 2H), 4.13-4.09 (m, 1H), 3.79-3.72 (m, 1H), 3.61-3.56 (m, 2H), 3.36-3.22 (m, 2H), 3.03-2.97 (m, 2H), 2.87 (s, 6H), 2.38-2.33 (m, 2H), 2.17-2.14 (m, 1H), 1.93-1.91 (m, 4H), 1.67-1.65 (m, 1H).

EXAMPLE 6



(3*S*,6*R*)-*N*-(Cyclopropylmethyl)-3-(2,3-difluorophenyl)-6-({[4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidin-1-yl]carbonyl}amino)azepane-1-carboxamide

Step A. (3*S*,6*R*)-3-(2,3-Difluorophenyl)-6-({[4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidin-1-yl]carbonyl}amino)azepane-1-carbonyl chloride

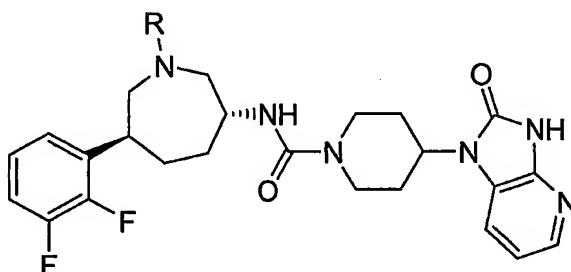
Triethylamine (104 μ L, 0.74 mmol) and phosgene (20% solution in toluene; 0.395 mL, 0.75 mmol) were sequentially added to a solution of *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)azepan-3-yl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide (0.35 g, 0.74 mmol) in dichloromethane (10 mL) at 0 $^{\circ}\text{C}$. After 30 min, the reaction mixture was quenched with water. The mixture was extracted with dichloromethane (3x), and the combined organic extracts were washed with saturated brine, dried over sodium sulfate, filtered and concentrated. MS 533.1 (*M*+1).

Step B. (3*S*,6*R*)-*N*-(Cyclopropylmethyl)-3-(2,3-difluorophenyl)-6-({[4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidin-1-yl]carbonyl}amino)azepane-1-carboxamide

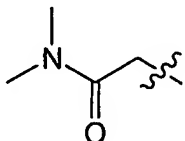
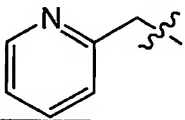
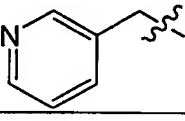

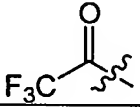
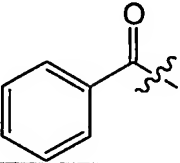
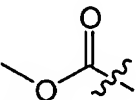
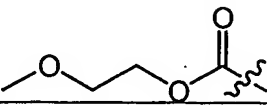
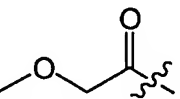
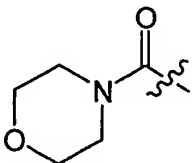
Diisopropylethylamine (13.0 μ L, 0.075 mmol) and cyclopropanemethylamine (13.0 μ L, 0.15 mmol) were sequentially added to a solution of (3*S*,6*R*)-3-(2,3-difluorophenyl)-6-({[4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidin-1-yl]carbonyl}amino)azepane-1-carbonyl chloride (20 mg, 0.038 mmol) in dichloromethane (1.2 mL). After 18 h, the reaction mixture was concentrated. Purification by reverse phase HPLC (C-18, 95% water/ acetonitrile \rightarrow 5% water/ acetonitrile with 0.1% trifluoroacetic acid) gave the title compound (15 mg). MS 568.2836 ($M+1$).

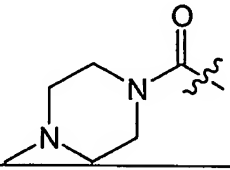
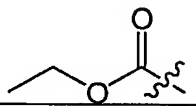
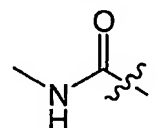
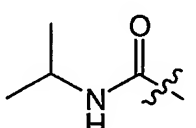
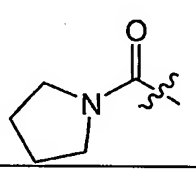
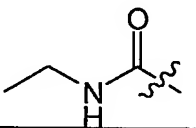
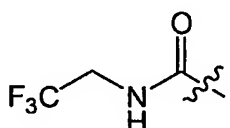
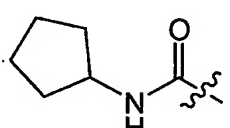
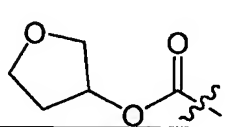
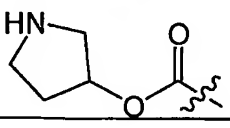
- 10 Essentially following the procedures outlined for the preparation of Examples 3-6, the Examples in Table 1 were prepared.

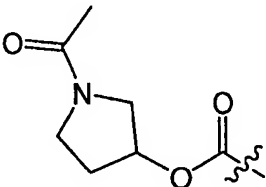
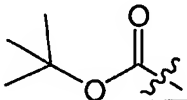
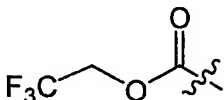
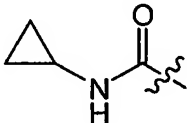
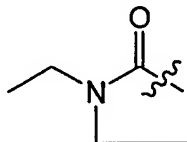
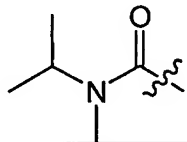
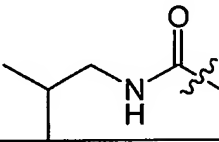
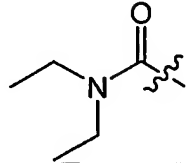
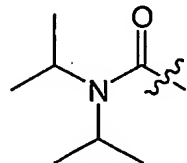
TABLE 1

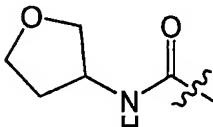
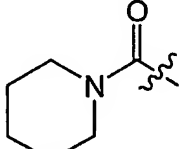
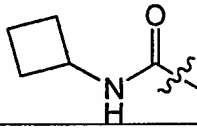
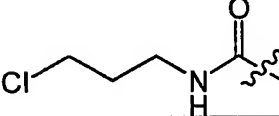
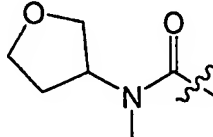
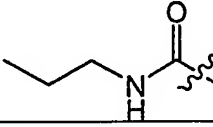
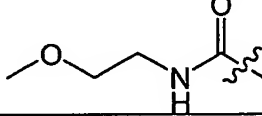
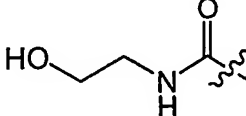
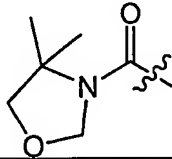


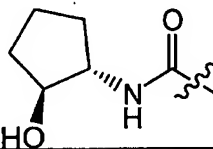
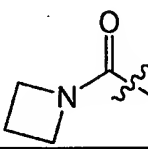
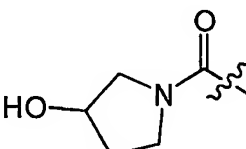
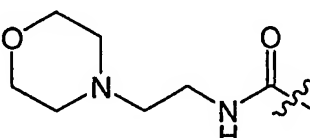
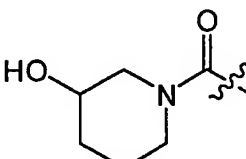
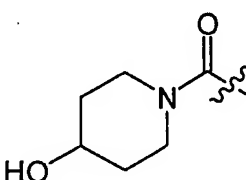
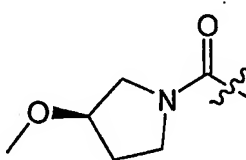
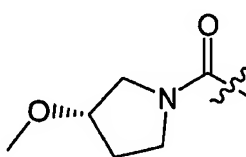
Example	R	MS ($M+1$)
7	CH ₃	485.2434
8		499.2957
9		553.2368
10		529.2744
11		529.1

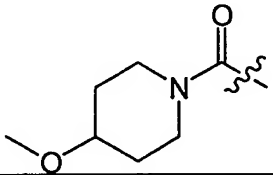
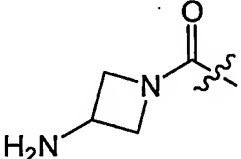
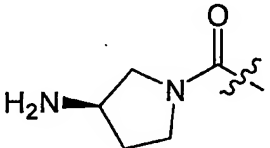
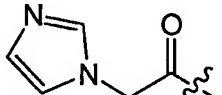
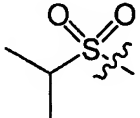
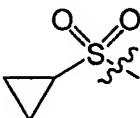
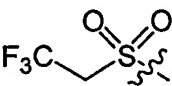
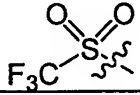
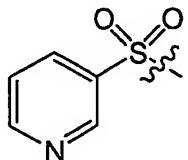
12	 <chem>CN(C)C(=O)C</chem>	556.1
13	 <chem>C1=CC=CC=N1C</chem>	562.2710
14	 <chem>C1=CC=CC=N1CC</chem>	562.2749
15	 <chem>CC(=O)C</chem>	513.2447
16	 <chem>CC(=O)C(F)(F)F</chem>	567.2146
17	 <chem>CC(=O)c1ccccc1</chem>	575.2553
18	 <chem>CC(=O)OC</chem>	529.2350
19	 <chem>CC(=O)OCCOC</chem>	573.2621
20	 <chem>CC(=O)OC</chem>	543.2515
21	 <chem>CC(=O)N1CCOCC1</chem>	584.2801

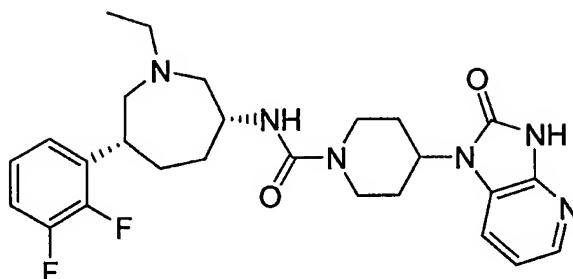
22		597.3113
23		543.2536
24		528.2526
25		556.2847
26		568.2842
27		542.2700
28		596.2
29		582.2950
30		585.2632
31		584.2802

32	 <chem>CC(=O)N1CCOC1=O</chem>	626.2907
33	 <chem>CC1(C)OC(C)(C)OC1=O</chem>	571.2856
34	 <chem>CC(=O)OCC(F)(F)F</chem>	597.2256
35	 <chem>CC(=O)NC1CC1</chem>	554.2682
36	 <chem>CCNC(=O)OCC</chem>	556.2821
37	 <chem>CC(C)NC(=O)OCC</chem>	570.2993
38	 <chem>CC(C)CNC(=O)OCC</chem>	570.2994
39	 <chem>CCNC(=O)OCC</chem>	570.2974
40	 <chem>CC(C)CNC(=O)OCC</chem>	598.3

41		584.273 6
42		582.300 5
43		568.279 2
44		590.245 7
45		598.295 8
46		556.282 9
47		572.277 7
48		558.263 0
49		598.293 0

50		598.2913
51		554.2685
52		584.2758
53		67.3207
54		598.2938
55		598.2947
56		598.2929
57		598.2940

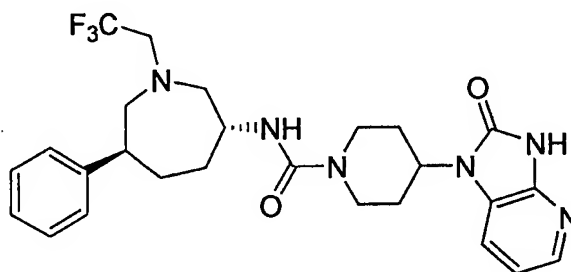
58	 <chem>COC1CCCN(C1)C(=O)C</chem>	612.3111
59	 <chem>N[C@@H]1CCN(C1)C(=O)C</chem>	569.2801
60	 <chem>N[C@H]1CCN(C1)C(=O)C</chem>	583.2937
61	 <chem>C1=CN=C(N1)CC(=O)C</chem>	579.2628
62	 <chem>CC(C)CS(=O)(=O)C</chem>	577
63	 <chem>C1CC1CS(=O)(=O)C</chem>	575.2213
64	 <chem>CC(F)(F)FCS(=O)(=O)C</chem>	617.1915
65	 <chem>FC(F)(F)S(=O)(=O)C</chem>	603.1790
66	 <chem>c1ccncc1S(=O)(=O)C</chem>	612.2199

EXAMPLE 67

5 *N*-[(3*R*,6*R*)-6-(2,3-difluorophenyl)-1-ethylazepan-3-yl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide

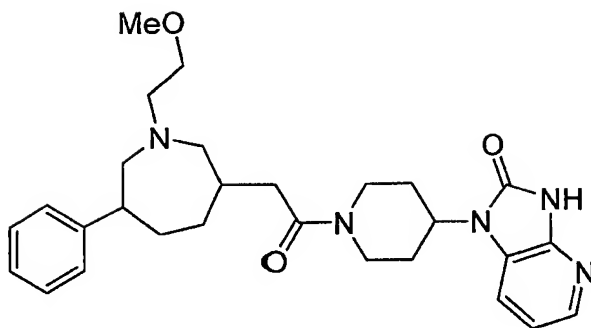
The title compound was prepared using a similar procedure to Example 3 starting with *tert*-butyl[(3*R*,6*R*)-6-(2,3-difluorophenyl)-2-oxoazepan-3-yl]carbamate. MS 499.2615 (M+1)

10

EXAMPLE 68

15 4-(2-Oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)-*N*-[(3*R*,6*S*)-6-phenyl-1-(2,2,2-trifluoroethyl)azepan-3-yl]piperidine-1-carboxamide

The title compound was prepared using a similar procedure to Example 3 starting with *tert*-butyl (3*R*,6*S*)-2-oxo-6-phenylazepan-3-ylcarbamate. MS 517.4 (M+1).

EXAMPLE 69

5 1-(1-([1-(2-Methoxyethyl)-6-phenylazepan-3-yl]acetyl)piperidin-4-yl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

Step A. *tert*-Butyl[1-(2-methoxyethyl)-6-phenylazepan-3-yl]acetate

Borane-THF (1.0 M in THF; 0.269 mL, 0.269 mmol) was added to a solution of *tert*-butyl [1-(2-methoxyethyl)-2-oxo-6-phenylazepan-3-yl]acetate (15 mg, 0.041 mmol) in tetrahydrofuran
10 (0.2 mL). After 65 h, the reaction was quenched with saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate (3x), and the combined organic extracts were washed with water, saturated brine, dried over sodium sulfate, filtered and concentrated. MS 348.2 (M+1).

Step B. [1-(2-Methoxyethyl)-6-phenylazepan-3-yl]acetic acid

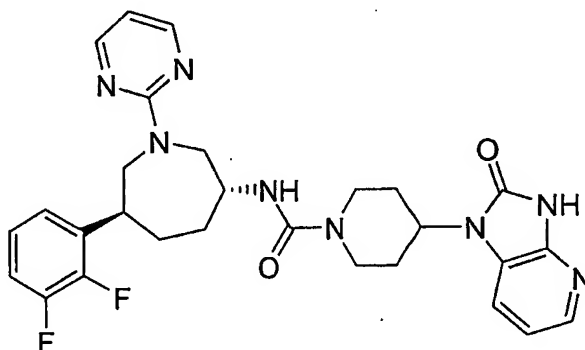
15 Trifluoroacetic acid (0.2 mL) was added to a solution of *tert*-butyl[1-(2-methoxyethyl)-6-phenylazepan-3-yl]acetate (10.0 mg, 0.029 mmol) in dichloromethane (1.0 mL). After 2 h, the solution was concentrated. Saturated aqueous sodium bicarbonate was added and the mixture was extracted with ethyl acetate (3x), and the combined organic extracts were washed with saturated brine, dried over sodium sulfate, filtered and concentrated. MS 292.3 (M+1).

20 Step C. 1-(1-([1-(2-Methoxyethyl)-6-phenylazepan-3-yl]acetyl)piperidin-4-yl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one

Triethylamine (16 μ L, 0.115 mmol) was added to a solution of [1-(2-methoxyethyl)-6-phenylazepan-3-yl]acetic acid (8.4 mg, 0.03 mmol), 2-oxo-1-piperidinium-4-yl-2,3-dihydro-1*H*-imidazo[4,5-b]pyridin-4-ium dichloride (8.0 mg, 0.03 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (11 mg, 0.06 mmol), and 1-hydroxybenzotriazole hydrate (4.0 mg, 0.03 mmol) in *N,N*-dimethylformamide (0.5 mL). After 18 h, the reaction was filtered. Purification by reverse phase HPLC (C-18, 95% water/ acetonitrile \rightarrow 5% water/ acetonitrile with 0.1% trifluoroacetic acid) gave the title compound (2.9 mg). MS 492.2 (M+1). ^1H NMR (500 MHz, CDCl_3) δ 8.67 (s, 1H), 8.07-8.03

(m, 1H), 7.25-7.20 (m, 5H), 7.06-7.00 (m, 1H), 4.92 (d, $J = 11.5$ Hz, 1H), 4.59 (br s, 1H), 4.15-4.12 (m, 1H), 3.51-3.49 (m, 2H), 3.35 (s, 3H), 3.25-3.21 (m, 1H), 3.05-2.96 (m, 3H), 2.93-2.86 (m, 2H), 2.72-2.67 (m, 2H), 2.66-2.53 (m, 2H), 2.40-2.33 (m, 2H), 2.30-2.21 (m, 2H), 2.19-1.89 (m, 6H).

5

EXAMPLE 70

N-[(3*R*,6*S*)-6-(2,3-Difluorophenyl)-1-pyrimidin-2-ylazepan-3-yl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-
b]pyridin-1-yl)piperidine-1-carboxamide

Step A. *tert*-Butyl (3*R*,6*S*)-6-(2,3-difluorophenyl)-1-pyrimidin-2-ylazepan-3-ylcarbamate

Cesium carbonate (60.0 mg, 0.18 mmol) was added to a suspension of *tert*-butyl (3*R*,6*S*)-6-(2,3-difluorophenyl)azepan-3-ylcarbamate (50.0 mg, 0.15 mmol), 2-bromopyrimidine (49.0 mg, 0.31 mmol), [5-(diphenylphosphino)-9,9-dimethyl-9*H*-xanthen-4-yl](diphenyl)phosphine (27.0 mg, 0.05 mmol), tris(dibenzylideneacetone) dipalladium (28.0 mg, 0.03 mmol) in dioxane (0.5 mL) and *N,N*-dimethylacetamide (0.1 mL), and the mixture heated at 120 °C in an Emrys optimizer microwave reactor for 1 h. Water was added the mixture was extracted with dichloromethane(3x), and the combined organic extracts were washed with saturated brine, dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography (100% hexanes → 60% ethyl acetate/ hexanes) gave the title compound (40 mg). MS 405.2 (M+1).

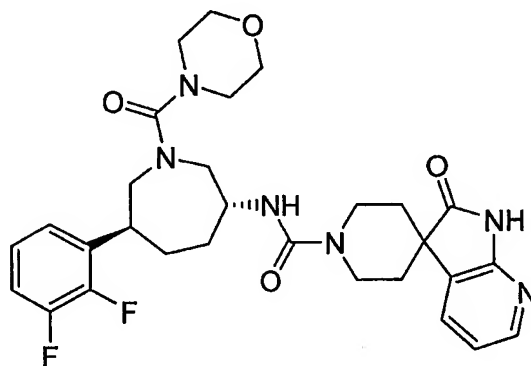
Step B. (3*R*,6*S*)-6-(2,3-Difluorophenyl)-1-pyrimidin-2-ylazepan-3-amine

Trifluoroacetic acid (1 mL) was added to a solution of *tert*-butyl (3*R*,6*S*)-6-(2,3-difluorophenyl)-1-pyrimidin-2-ylazepan-3-ylcarbamate (40 mg, 0.10 mmol) in dichloromethane (2 mL). After 18 h, saturated aqueous sodium bicarbonate was added. The mixture was extracted with dichloromethane (3x), and the combined organic extracts were washed with saturated brine, dried over sodium sulfate, filtered and concentrated. MS 305.1 (M+1).

Step C. *N*-[(3*R*,6*S*)-6-(2,3-Difluorophenyl)-1-pyrimidin-2-ylazepan-3-yl]-4-(2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-1-yl)piperidine-1-carboxamide

Triethylamine (14.0 μ L, 0.10 mmol) was added to a solution of (3*R*,6*S*)-6-(2,3-difluorophenyl)-1-pyrimidin-2-ylazepan-3-amine (40.0 mg, 0.10 mmol) and 4-nitrophenyl chloroformate (20.0 mg, 0.10 mmol) in tetrahydrofuran (2 mL) at 0 $^{\circ}$ C. After 1 h, 2-oxo-1-piperidinium-4-yl-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-4-ium dichloride (29.0 mg, 0.10 mmol) and triethylamine (42 μ L, 0.30 mmol) were added and the mixture allowed to warm to ambient temperature. After 18 h, saturated aqueous sodium carbonate was added and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate (3x), saturated brine, dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography [100% dichloromethane \rightarrow 90% dichloromethane/ 10% (10% ammonium hydroxide/ methanol)] gave the title compound. MS 549.25 32 (M+1). The title compound was converted to the HCl salt with 2M HCl in ether. 1 H NMR (500 MHz, CD₃OD) δ 8.91 (s, 1H), 8.61 (s, 1H), 8.02 (d, *J* = 5.9 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.0 Hz, 1H), 7.24-7.20 (m, 1H), 7.20 (d, *J* = 4.9 Hz, 2H), 7.12 (t, *J* = 5.3 Hz, 1H), 4.57-4.52 (m, 1H), 4.43-4.38 (m, 3H), 3.94 (d, *J* = 14.9 Hz, 1H), 3.84-3.79 (m, 1H), 3.75-3.70 (m, 3H), 3.10-3.04 (m, 2H), 2.45-2.38 (m, 2H), 2.20-2.18 (m, 1H), 2.10-2.02 (m, 2H), 1.96-1.94 (m, 2H), 1.91-1.87 (m, 1H).

EXAMPLE 71



N-[(3*R*,6*S*)-6-(2,3-Difluorophenyl)-1-(morpholin-4-ylcarbonyl)azepan-3-yl]-2'-oxo-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*b*]pyridine]-1-carboxamide

Step A. Benzyl (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)azepane-1-carboxylate

Trifluoroacetic acid (1 mL) was added to a solution benzyl (3*R*,6*S*)-3-[(tert-butoxycarbonyl)amino]-6-(2,3-difluorophenyl)azepane-1-carboxylate

(200 mg, 0.434 mmol) in dichloromethane (2 mL). After 18 h, saturated sodium bicarbonate was added. The mixture was extracted with dichloromethane (3x), and the combined organic extracts were washed with saturated brine, dried over sodium sulfate, filtered and concentrated. MS 361.1 (M+1).

5 Step B. Benzyl (3*S*,6*R*)-3-(2,3-difluorophenyl)-6-([(2'-oxo-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*b*]pyridin]-1-yl)carbonyl]amino)azepane-1-carboxylate

Triethylamine (61 μ L, 0.434 mmol) was added to a solution of benzyl (3*R*,6*S*)-3-amino-6-(2,3-difluorophenyl)azepane-1-carboxylate (156 mg, 0.434 mmol) and 4-nitrophenyl chloroformate (88 mg, 0.434 mmol) in tetrahydrofuran (3 mL) at 0 °C. After 1 h, 2'-oxo-1',2'-dihydrospiro[piperidine-4,3'-pyrrolo[2,3-*b*]pyridine] dichloride (120 mg, 0.434 mmol) and triethylamine (183 μ L, 1.30 mmol) were added and the mixture allowed to warm to ambient temperature. After 18 h, saturated aqueous sodium carbonate was added and the mixture was extracted with dichloromethane. The organic layer was washed with saturated aqueous sodium bicarbonate (3x), saturated brine, dried over sodium sulfate, filtered and concentrated. Purification by silica gel chromatography [100% dichloromethane \rightarrow 93% dichloromethane/ methanol] gave the title compound (156 mg). MS 590.2 (M+1).

Step C. *N*-[(3*R*,6*S*)-6-(2,3-Difluorophenyl)azepan-3-yl]-2'-oxo-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*b*]pyridine]-1-carboxamide

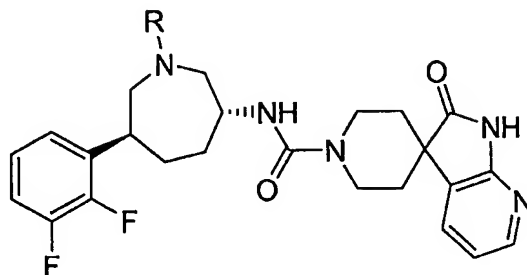
10% palladium on carbon (30 mg) was added to a solution of benzyl (3*S*,6*R*)-3-(2,3-difluorophenyl)-6-([(2'-oxo-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*b*]pyridin]-1-yl)carbonyl]amino)azepane-1-carboxylate (156 mg, 0.265 mmol) in methanol (5 mL). The reaction vessel was evacuated and back-filled with nitrogen (3x), then back-filled with hydrogen (1 atm). After 65 h, the mixture was filtered with celite and concentrated. MS 456.1 (M+1).

25 Step D. *N*-[(3*R*,6*S*)-6-(2,3-Difluorophenyl)-1-(morpholin-4-ylcarbonyl)azepan-3-yl]-2'-oxo-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*b*]pyridine]-1-carboxamide

4-Morpholinecarbonyl chloride (4.0 μ L, 0.033 mmol) and diisopropylethylamine (6.0 μ L, 0.033 mmol) were added to a solution of *N*-[(3*R*,6*S*)-6-(2,3-difluorophenyl)azepan-3-yl]-2'-oxo-1',2'-dihydro-1*H*-spiro[piperidine-4,3'-pyrrolo[2,3-*b*]pyridine]-1-carboxamide (15 mg, 0.033 mmol) in dichloromethane (1 mL). After 18 h, additional 4-morpholinecarbonyl chloride (80 μ L, 0.66 mmol) and diisopropylethylamine (120 μ L, 0.66 mmol) were added and the reaction mixture was heated to 40 °C. After 3 h, the reaction mixture was concentrated. Purification by reverse phase HPLC (C-18, 95% water/ acetonitrile \rightarrow 5% water/ acetonitrile with 0.1% trifluoroacetic acid) gave the title compound (2.0 mg). MS 569.2665 (M+1).

Essentially following the procedures outlined for the preparation of Example 71, the Examples in Table 2 were prepared.

TABLE 2

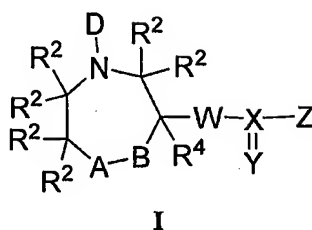


Example	R	MS (M+1)
72		484.2527
73		553.2742
74		514.2265

While the invention has been described and illustrated with reference to certain particular embodiments thereof, those skilled in the art will appreciate that various adaptations, changes, modifications, substitutions, deletions, or additions of procedures and protocols may be made without departing from the spirit and scope of the invention. For example, effective dosages other than the particular dosages as set forth herein above may be applicable as a consequence of variations in the responsiveness of the mammal being treated for any of the indications with the compounds of the invention indicated above. Likewise, the specific pharmacological responses observed may vary according to and depending upon the particular active compounds selected or whether there are present pharmaceutical carriers, as well as the type of formulation and mode of administration employed, and such expected variations or differences in the results are contemplated in accordance with the objects and practices of the present invention. It is intended, therefore, that the invention be defined by the scope of the claims which follow and that such claims be interpreted as broadly as is reasonable.

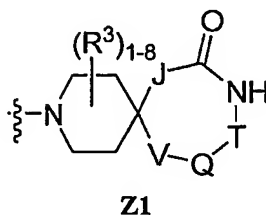
WHAT IS CLAIMED IS:

1. A compound of Formula I:

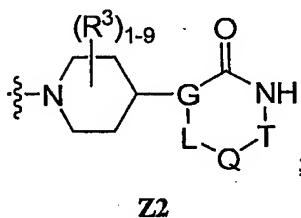


wherein:

Z is selected from:



and



A is a bond, $C(R^2)_2$, O, $S(O)_m$ or NR^2 ;

20 B is $(C(R^2)_2)_n$;

D is selected from R^1 , OR^1 , $N(R^1)_2$, $NR^1C(O)R^1$, $C(O)R^1$, $S(O)_mR^1$, $C(O)OR^1$, $C(O)N(R^1)_2$, $C(O)NR^{10}R^{11}$, $C(NR^1)N(R^1)_2$, and $C(NR^1)R^1$;

25 R^1 is independently selected from:

- 1) H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-6 cycloalkyl, and hetero cycle, unsubstituted or substituted with one or more substituents each independently selected from:

- a) C₁-6 alkyl,
- b) C₃-6 cycloalkyl,
- c) aryl, unsubstituted or substituted with 1-5 substituents each independently selected from R⁴,
- d) heteroaryl, unsubstituted or substituted with 1-5 substituents each independently selected from R⁴,
- e) heterocycle, unsubstituted or substituted with 1-5 substituents each independently selected from R⁴,
- f) (F)_pC₁₋₃ alkyl,
- g) halogen,
- h) OR⁴,
- i) O(CH₂)_s OR⁴,
- j) CO₂R⁴,
- k) (CO)NR¹⁰R¹¹,
- l) O(CO)NR¹⁰R¹¹,
- m) N(R⁴)(CO)NR¹⁰R¹¹,
- n) N(R¹⁰)(CO)R¹¹,
- o) N(R¹⁰)(CO)OR¹¹,
- p) SO₂NR¹⁰R¹¹,
- q) N(R¹⁰) SO₂R¹¹,
- r) S(O)_mR¹⁰,
- s) CN,
- t) NR¹⁰R¹¹,
- u) N(R¹⁰)(CO)NR⁴R¹¹, and,
- v) O(CO)R⁴, and

- 2) aryl or heteroaryl, unsubstituted or substituted with one or more substituents each independently selected from:

- a) C₁-6 alkyl,
- b) C₃-6 cycloalkyl,

- 5 c) aryl, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
 d) heteroaryl, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
 e) heterocycle, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
 f) $(F)_p C_{1-3}$ alkyl,
 g) halogen,
 h) OR^4 ,
 10 i) $O(CH_2)_s OR^4$,
 j) $CO_2 R^4$,
 k) $(CO)NR^{10}R^{11}$,
 l) $O(CO)NR^{10}R^{11}$,
 m) $N(R^4)(CO)NR^{10}R^{11}$,
 15 n) $N(R^{10})(CO)R^{11}$,
 o) $N(R^{10})(CO)OR^{11}$,
 p) $SO_2 NR^{10}R^{11}$,
 q) $N(R^{10}) SO_2 R^{11}$,
 r) $S(O)_m R^{10}$,
 20 s) CN ,
 w) $NR^{10}R^{11}$,
 x) $N(R^{10})(CO)NR^4 R^{11}$, and
 y) $O(CO)R^4$;

25 R^1 can be optionally joined to R^2 to form a 4-8 membered ring;

R^2 is independently selected from:

- 30 1) H , C_0 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl and heterocycle, unsubstituted or substituted with one or more substituents each independently selected from:
 a) C_{1-6} alkyl,
 b) C_{3-6} cycloalkyl,

- 5 c) aryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4 ,
d) heteroaryl, unsubstituted or substituted with 1-5 substituents each independently
selected from R^4 ,
e) heterocycle, unsubstituted or substituted with 1-5 substituents each independently
selected from R^4 ,
f) $(F)_p C_{1-3}$ alkyl,
g) halogen,
h) OR^4 ,
10 i) $O(CH_2)_s OR^4$,
j) $CO_2 R^4$,
k) $(CO)NR^{10}R^{11}$,
l) $O(CO)NR^{10}R^{11}$,
m) $N(R^4)(CO)NR^{10}R^{11}$,
15 n) $N(R^{10})(CO)R^{11}$,
o) $N(R^{10})(CO)OR^{11}$,
p) $SO_2 NR^{10}R^{11}$,
q) $N(R^{10}) SO_2 R^{11}$,
r) $S(O)_m R^{10}$,
20 s) CN ,
t) $NR^{10}R^{11}$,
u) $N(R^{10})(CO)NR^4 R^{11}$, and,
v) $O(CO)R^4$, and
- 25 2) aryl or heteroaryl, unsubstituted or substituted with one or more substituents each
independently selected from:
- a) C_{1-6} alkyl,
b) C_{3-6} cycloalkyl,
30 c) aryl, unsubstituted or substituted with 1-5 substituents where the substituents are
independently selected from R^4 ,
d) heteroaryl, unsubstituted or substituted with 1-5 substituents each independently
selected from R^4 ,
e) heterocycle, unsubstituted or substituted with 1-5 substituents each independently
35 selected from R^4 ,

- 5 f) (F)_pC₁₋₃ alkyl,
 g) halogen,
 h) OR⁴,
 i) O(CH₂)_sOR⁴,
 j) CO₂R⁴,
 k) (CO)NR¹⁰R¹¹,
 l) O(CO)NR¹⁰R¹¹,
 m) N(R⁴)(CO)NR¹⁰R¹¹,
 n) N(R¹⁰)(CO)R¹¹,
 10 o) N(R¹⁰)(CO)OR¹¹,
 p) SO₂NR¹⁰R¹¹,
 q) N(R¹⁰)SO₂R¹¹,
 r) S(O)_mR¹⁰,
 s) CN,
 15 t) NR¹⁰R¹¹,
 u) N(R¹⁰)(CO)NR⁴R¹¹, and
 v) O(CO)R⁴,

20 where any two independent R² on the same or adjacent atoms optionally join to form a ring selected from cyclobutyl, cyclopentenyl, cyclopentyl, cyclohexenyl, cyclohexyl, phenyl, naphthyl, thienyl, thiazolyl, thiazoliny, oxazolyl, oxazoliny, imidazolyl, imidazoliny, imidazolidiny, pyridyl, pyrimidyl, pyrazinyl, pyrrolyl, pyrroliny, morpholiny, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S-dioxide, azetidiny, pyrrolidiny, piperidiny, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridyl, furanyl, dihydrofuranyl, dihydropyranyl
 25 and piperazinyl;

R¹⁰ and R¹¹ are each independently selected from: H, C₁₋₆ alkyl, (F)_pC₁₋₆ alkyl, C₃₋₆ cycloalkyl, aryl, heteroaryl, and benzyl, unsubstituted or substituted with halogen, hydroxy or C₁₋₆ alkoxy, where R¹⁰ and R¹¹ optionally join to form a ring selected from: azetidiny, pyrrolidiny, piperidiny, piperazinyl, and
 30 morpholiny, which is ring is unsubstituted or substituted with 1-5 substituents each independently selected from R⁴;

R⁴ is independently selected from: H, C₁₋₆ alkyl, (F)_pC₁₋₆ alkyl, C₃₋₆ cycloalkyl, aryl, heteroaryl and benzyl, unsubstituted or substituted with halogen, hydroxy or C₁₋₆ alkoxy;

35

W is O, NR^4 or $\text{C}(\text{R}^4)_2$;

X is C or S;

5 Y is O, $(\text{R}^4)_2$, NCN , NSO_2CH_3 or NCONH_2 , or Y is O_2 when X is S;

R^6 is independently selected from H and:

- a) C_{1-6} alkyl,
- 10 b) C_{3-6} cycloalkyl,
- c) aryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4 ,
- d) heteroaryl, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
- 15 e) heterocycle, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
- f) $(\text{F})_p\text{C}_{1-3}$ alkyl,
- g) halogen,
- h) OR^4 .
- 20 i) $\text{O}(\text{CH}_2)_5\text{OR}^4$,
- j) CO_2R^4 ,
- k) $(\text{CO})\text{NR}^{10}\text{R}^{11}$,
- l) $\text{O}(\text{CO})\text{NR}^{10}\text{R}^{11}$,
- m) $\text{N}(\text{R}^4)(\text{CO})\text{NR}^{10}\text{R}^{11}$,
- 25 n) $\text{N}(\text{R}^{10})(\text{CO})\text{R}^{11}$,
- o) $\text{N}(\text{R}^{10})(\text{CO})\text{OR}^{11}$,
- p) $\text{SO}_2\text{NR}^{10}\text{R}^{11}$,
- q) $\text{N}(\text{R}^{10})\text{SO}_2\text{R}^{11}$,
- r) $\text{S}(\text{O})_m\text{R}^{10}$,
- 30 s) CN ,
- t) $\text{NR}^{10}\text{R}^{11}$,
- u) $\text{N}(\text{R}^{10})(\text{CO})\text{NR}^4\text{R}^{11}$, and
- v) $\text{O}(\text{CO})\text{R}^4$;

35 J is a bond, $\text{C}(\text{R}^6)_2$, O or NR^6 ;

V is selected from a bond, $C(R^6)_2$, O, $S(O)_m$, NR^6 , $C(R^6)_2-C(R^6)_2$, $C(R^6)=C(R^6)$, $C(R^6)_2-N(R^6)$, $C(R^6)=N$, $N(R^6)-C(R^6)_2$, $N=C(R^6)$, and $N(R^6)-N(R^6)$;

5 G-L is selected from: N, $N-C(R^6)_2$, $C=C(R^6)$, $C=N$, $C(R^6)$, $C(R^6)-C(R^6)_2$, $C(R^6)-C(R^6)_2-C(R^6)_2$, $C=C(R^6)-C(R^6)_2$, $C(R^6)-C(R^6)=C(R^6)$, $C(R^6)-C(R^6)_2-N(R^6)$, $C=C(R^6)-N(R^6)$, $C(R^6)-C(R^6)=N$, $C(R^6)-N(R^6)-C(R^6)_2$, $C=N-C(R^6)_2$, $C(R^6)-N=C(R^6)$, $C(R^6)-N(R^6)-N(R^6)$, $C=N-N(R^6)$, $N-C(R^6)_2-C(R^6)_2$, $N-C(R^6)=C(R^6)$, $N-C(R^6)_2-N(R^6)$, $N-C(R^6)=N$, $N-N(R^6)-C(R^6)_2$ and $N-N=C(R^6)$;

10 Q is selected from:

- (1) $=C(R^{7a})-$,
- (2) $-C(R^{7a})_2-$,
- (3) $-C(=O)-$,
- (4) $-S(O)_m-$,

15 (5) $=N-$, and
(6) $-N(R^{7a})-$;

T is selected from:

- (1) $=C(R^{7b})-$,
- 20 (2) $-C(R^{7b})_2-$,
- (3) $-C(=O)-$,
- (4) $-S(O)_m-$,
- (5) $=N-$, and
- (6) $-N(R^{7b})-$;

25

R^3 is independently selected from H, substituted or unsubstituted C_1-C_3 alkyl, F, CN and CO_2R^4 ;

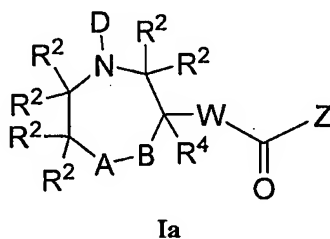
R^{7a} and R^{7b} are each independently selected from R^2 , where R^{7a} and R^{7b} and the atom or atoms to which they are attached optionally join to form a ring selected from C_3-6 cycloalkyl, aryl, heterocycle, and heteroaryl, which ring is unsubstituted or substituted with 1-10 substituents each independently
30 selected from R^6 ;

p is 0 to $2q+1$, for a substituent with q carbons;
m is 0, 1 or 2;
n is 0 or 1;
s is 1, 2 or 3;

and pharmaceutically acceptable salts and individual diastereomers thereof.

2. A compound of claim 1 having the formula Ia:

5

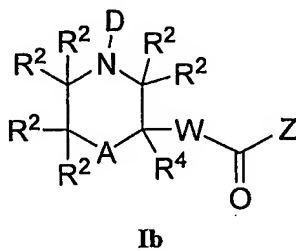


wherein:

- 10 A is a bond, $C(R^2)_2$, O, $S(O)_m$ or NR^2 ;
 B is $(C(R^2)_2)_n$;
 n is 0 or 1; and
 and pharmaceutically acceptable salts and individual stereoisomers thereof.

15

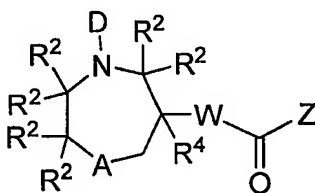
3. A compound of claim 1 having the formula Ib:



wherein:

- 20 A is $C(R^2)_2$, O, $S(O)_m$ or NR^2 ;
 and pharmaceutically acceptable salts and individual stereoisomers thereof.

4. A compound of claim 1 having the formula Ic:



25

Ic

wherein:

A is $C(R^2)_2$, O, $S(O)_m$ or NR^2 ;

5 and pharmaceutically acceptable salts and individual stereoisomers thereof.

5. The compound of claim 1, wherein:

10 D is selected from R^1 , OR^1 , $N(R^1)_2$, $NR^1C(O)R^1$, $C(O)R^1$, $S(O)_mR^1$, $C(O)OR^1$, $C(O)N(R^1)_2$, $C(O)NR^{10}R^{11}$, $C(NR^1)N(R^1)_2$ and $C(NR^1)R^1$;

R^1 is selected from:

- 15 1) H, C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl and heterocycle, unsubstituted or substituted with one or more substituents each independently selected from:
 - a) C_1 - C_6 alkyl,
 - b) C_3 - C_6 cycloalkyl,
 - 20 c) aryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4 ,
 - d) heteroaryl, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
 - e) heterocycle, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
 - 25 f) $(F)_pC_{1-3}$ alkyl,
 - g) halogen,
 - h) OR^4 .
 - i) $O(CH_2)_sOR^4$,
 - j) CO_2R^4 ,
 - 30 k) CN,
 - l) $NR^{10}R^{11}$, and
 - m) $O(CO)R^4$; and
- 35 2) aryl or heteroaryl, unsubstituted or substituted with one or more substituents independently selected from:

- 5
- a) C₁₋₆ alkyl,
 - b) C₃₋₆ cycloalkyl,
 - c) (F)_pC₁₋₃ alkyl,
 - d) halogen,
 - e) OR⁴,
 - f) CO₂R⁴,
 - g) (CO)NR¹⁰R¹¹,
 - h) SO₂NR¹⁰R¹¹,
 - i) N(R¹⁰)SO₂R¹¹,
 - 10 j) S(O)_mR⁴,
 - k) CN,
 - l) NR¹⁰R¹¹, and,
 - m) O(CO)R⁴;

15 R² is selected from:

- 1) H, C₀-C₆ alkyl, C₂-C₆ alkynyl, C₃₋₆ cycloalkyl and heterocycle, unsubstituted or substituted with one or more substituents each independently selected from:

- 20
- a) C₁₋₆ alkyl,
 - b) C₃₋₆ cycloalkyl,
 - c) aryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R⁴,
 - d) heteroaryl, unsubstituted or substituted with 1-5 substituents each independently
 - 25 selected from R⁴,
 - e) heterocycle, unsubstituted or substituted with 1-5 substituents each independently selected from R⁴,
 - f) (F)_pC₁₋₃ alkyl,
 - g) halogen,
 - 30 h) OR⁴,
 - i) O(CH₂)_sOR⁴,
 - j) CO₂R⁴,
 - k) S(O)_mR⁴,
 - l) CN,
 - 35 m) NR¹⁰R¹¹, and

n) $O(CO)R^4$; and

2) aryl or heteroaryl, unsubstituted or substituted with one more substituents independently selected from:

- a) C_{1-6} alkyl,
- b) C_{3-6} cycloalkyl,
- c) $(F)_pC_{1-3}$ alkyl,
- d) halogen,
- e) OR^4 ,
- f) CO_2R^4 ,
- g) $(CO)NR^{10}R^{11}$,
- h) $SO_2NR^{10}R^{11}$,
- i) $N(R^{10})SO_2R^{11}$,
- j) $S(O)_mR^4$,
- k) CN ,
- l) $NR^{10}R^{11}$, and
- m) $O(CO)R^4$,

where any two independent R^2 on the same or adjacent atoms optionally join to form a ring selected from cyclobutyl, cyclopentenyl, cyclopentyl, cyclohexenyl, cyclohexyl, phenyl, naphthyl, thienyl, thiazolyl, thiazoliny, oxazolyl, oxazoliny, imidazolyl, imidazoliny, imidazolidiny, pyridyl, pyrimidyl, pyrazinyl, pyrrolyl, pyrroliny, morpholiny, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S-dioxide, azetidiny, pyrrolidiny, piperidiny, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridyl, furanyl, dihydrofuranyl, dihydropyranyl and piperaziny;

R^{10} and R^{11} are independently selected from: H, C_{1-6} alkyl, $(F)_pC_{1-6}$ alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl and benzyl, unsubstituted or substituted with halogen, hydroxy or C_{1-6} alkoxy, where R^{10} and R^{11} optionally join to form a ring selected from: azetidiny, pyrrolidiny, piperidiny, piperaziny and morpholiny, which ring is unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ;

R^4 is independently selected from: H, C_{1-6} alkyl, $(F)_pC_{1-6}$ alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl and benzyl, unsubstituted or substituted with halogen, hydroxy or C_{1-6} alkoxy;

W is O, NR^4 or $\text{C}(\text{R}^4)_2$;

R^6 is independently selected from H and:

5

- a) C_{1-6} alkyl,
- b) C_{3-6} cycloalkyl,
- c) $(\text{F})_p\text{C}_{1-3}$ alkyl,
- d) halogen,
- e) OR^4 .
- f) CO_2R^4 .
- g) $(\text{CO})\text{NR}^{10}\text{R}^{11}$,
- h) $\text{SO}_2\text{NR}^{10}\text{R}^{11}$,
- i) $\text{N}(\text{R}^{10})\text{SO}_2\text{R}^{11}$,
- j) $\text{S}(\text{O})_m\text{R}^4$,
- k) CN ,
- l) $\text{NR}^{10}\text{R}^{11}$ and
- m) $\text{O}(\text{CO})\text{R}^4$;

10

15

20 Z is Z1 and:

J is a bond and V is a bond, or

J is a bond, V is a bond and T is $-\text{C}(=\text{O})-$, or

25

J is a bond, V is a bond, $\text{C}(\text{R}^6)_2$, O, $\text{S}(\text{O})_m$, NR^6 , $\text{C}(\text{R}^6)_2-\text{C}(\text{R}^6)_2$, $\text{C}(\text{R}^6)=\text{C}(\text{R}^6)$, $\text{C}(\text{R}^6)_2-\text{N}(\text{R}^6)$, $\text{C}(\text{R}^6)=\text{N}$, $\text{N}(\text{R}^6)-\text{C}(\text{R}^6)_2$, $\text{N}=\text{C}(\text{R}^6)$ or $\text{N}(\text{R}^6)-\text{N}(\text{R}^6)$, or

J is a bond, $\text{C}(\text{R}^5)_2$, O, or NR^5 , V is a bond,

30

or Z is Z2 and G-L is selected from N, $\text{N}-\text{C}(\text{R}^6)_2$, $\text{C}=\text{C}(\text{R}^6)$, $\text{C}=\text{N}$ and $\text{N}-\text{C}(\text{R}^6)_2-\text{C}(\text{R}^6)_2$;

Q is selected from:

- (1) $=\text{C}(\text{R}^{7a})-$,
- (2) $-\text{C}(\text{R}^{7a})_2-$,

35

- (3) -C(=O)-,
- (4) -S(O)_m-,
- (5) =N-, and
- (6) -N(R^{7a})-;

5

T is selected from:

- (1) =C(R^{7b})-,
- (2) -C(R^{7b})₂-,
- (3) -C(=O)-,
- (4) -S(O)_m-,
- (5) =N-, and
- (6) -N(R^{7b})-;

10

R³ is independently selected from H, substituted or unsubstituted C₁-C₃ alkyl, F, CN and CO₂R⁴;

- 15 R^{7a} and R^{7b} are each independently selected from R², where R^{7a} and R^{7b} and the atom or atoms to which they are attached optionally join to form a ring selected from C₃-6 cycloalkyl, aryl, heterocycle, and heteroaryl, which ring is unsubstituted or substituted with 1-10 substituents each each independently selected from R⁶;

p is 0 to 2q+1, for a substituent with q carbons

20

m is 0 to 2;

s is 1 to 3;

and pharmaceutically acceptable salts and individual stereoisomers thereof.

25

6. The compound of claim 1, wherein:

R¹ is selected from:

- 1) H, C₁-C₆ alkyl, C₃-6 cycloalkyl and heterocycle, unsubstituted or substituted with one or more substituents each independently selected from:

30

- a) C₁-6 alkyl,
- b) C₃-6 cycloalkyl,
- c) phenyl, unsubstituted or substituted with 1-5 substituents

- each independently selected from R^4 ,
- d) heteroaryl, unsubstituted or substituted with 1-5 substituents
each independently selected from R^4 ,
and where heteroaryl is selected from:
- 5 imidazole, isoxazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine,
pyrimidine, and thiazole;
- e) heterocycle, unsubstituted or substituted with 1-5 substituents each independently
selected from R^4 , and where heterocycle is selected from: azetidine, dioxane,
dioxolane, morpholine, oxetane, piperazine, piperidine, pyrrolidine,
- 10 tetrahydrofuran, and tetrahydropyran;
- f) $(F)_pC_{1-3}$ alkyl,
- g) halogen,
- h) OR^4 .
- i) $O(CH_2)_nOR^4$.
- 15 j) CO_2R^4 .
- k) CN,
- l) $NR^{10}R^{11}$, and
- m) $O(CO)R^4$, and
- 20 2) aryl or heteroaryl, selected from: phenyl, imidazole, isoxazole, oxazole, pyrazine,
pyrazole, pyridazine, pyridine, pyrimidine, and thiazole,
unsubstituted or substituted with one or more substituents each independently selected
from:
- 25 a) C_{1-6} alkyl,
- b) C_{3-6} cycloalkyl,
- c) $(F)_pC_{1-3}$ alkyl,
- d) halogen,
- e) OR^4 .
- 30 f) CO_2R^4 .
- g) $(CO)NR^{10}R^{11}$.
- h) $SO_2NR^{10}R^{11}$.
- i) $N(R^{10})SO_2R^{11}$.
- j) $S(O)_mR^4$,
- 35 k) CN,

- l) $\text{NR}^{10}\text{R}^{11}$, and
- m) $\text{O}(\text{CO})\text{R}^4$;

R^2 is selected from:

5

- 1) H , $\text{C}_0\text{-C}_6$ alkyl, C_{3-6} cycloalkyl and heterocycle, unsubstituted or substituted with one or more substituents each independently selected from:

10

- a) C_{1-6} alkyl,
- b) C_{3-6} cycloalkyl,
- c) phenyl, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
- d) heteroaryl, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,

15

and where heteroaryl is selected from: benzimidazole, benzothiophene, furan, imidazole, indole, isoxazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, thiazole, thiophene, and triazole;

20

- e) heterocycle, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4 , and where heterocycle is selected from: azetidine, imidazolidine, imidazoline, isoxazoline, isoxazolidine, morpholine, oxazoline, oxazolidine, oxetane, pyrazolidine, pyrazoline, pyrroline, tetrahydrofuran, tetrahydropyran, thiazoline, and thiazolidine;

25

- f) $(\text{F})_p\text{C}_{1-3}$ alkyl,
- g) halogen,
- h) OR^4 .
- i) $\text{O}(\text{CH}_2)_s\text{OR}^4$,
- j) CO_2R^4 .
- k) CN ,
- l) $\text{NR}^{10}\text{R}^{11}$, and
- m) $\text{O}(\text{CO})\text{R}^4$; and

30

- 2) aryl or heteroaryl, selected from: phenyl, benzimidazole, benzothiophene, furan, imidazole, indole, isoxazole, oxazole, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, thiazole, thiophene, and

triazole, unsubstituted or substituted with one or more substituents each independently selected from:

- a) C₁₋₆ alkyl,
- b) C₃₋₆ cycloalkyl,
- c) (F)_pC₁₋₃ alkyl,
- d) halogen,
- e) OR⁴,
- f) CO₂R⁴,
- g) (CO)NR¹⁰R¹¹,
- h) SO₂NR¹⁰R¹¹,
- i) N(R¹⁰)SO₂R¹¹,
- j) S(O)_mR⁴,
- k) CN,
- l) NR¹⁰R¹¹, and
- m) O(CO)R⁴,

where any two independent R² on the same or adjacent atoms optionally join to form a ring selected from cyclobutyl, cyclopentenyl, cyclopentyl, cyclohexenyl, cyclohexyl, phenyl, naphthyl, thienyl, thiazolyl, thiazolyl, oxazolyl, oxazolyl, imidazolyl, imidazolyl, imidazolidinyl, pyridyl, pyrimidyl, pyrazinyl, pyrrolyl, pyrrolinyl, morpholinyl, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S-dioxide, azetidyl, pyrrolidinyl, piperidinyl, tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridyl, furanyl, dihydrofuranyl, dihydropyranyl and piperazinyl,

R¹⁰ and R¹¹ are each independently selected from: H, C₁₋₆ alkyl, (F)_pC₁₋₆ alkyl, C₃₋₆ cycloalkyl, aryl, heteroaryl and benzyl, unsubstituted or substituted with halogen, hydroxy or C_{1-C6} alkoxy, where R¹⁰ and R¹¹ optionally join to form a ring selected from: azetidyl, pyrrolidinyl, piperidinyl, piperazinyl and morpholinyl, which ring is unsubstituted or substituted with 1-5 substituents each independently selected from R⁴;

R⁴ is independently selected from: H, C₁₋₆ alkyl, (F)_pC₁₋₆ alkyl, C₃₋₆ cycloalkyl, aryl, heteroaryl and phenyl, unsubstituted or substituted with hydroxy or C_{1-C6} alkoxy;

W is NR⁴ or C(R⁴)₂;

R⁶ is independently selected from H and:

- 5 a) C₁₋₆ alkyl,
 b) C₃₋₆ cycloalkyl,
 c) (F)_pC₁₋₃ alkyl,
 d) halogen,
 e) OR⁴.
 f) CO₂R⁴.
 10 g) (CO)NR¹⁰R¹¹.
 h) SO₂NR¹⁰R¹¹.
 i) N(R¹⁰) SO₂R¹¹.
 j) S(O)_mR⁴.
 k) CN,
 15 l) NR¹⁰R¹¹, and
 m) O(CO)R⁴;

Z is Z1 and:

20 J is a bond, V is a bond, Q is -N(R^{7a})-, and T is -C(=O)-, or

J is a bond, V is a bond, Q is -C(R^{7a})₂-, and T is -C(=O)-, or

J is a bond, V is a bond, Q is -N=, and T is =C(R^{7b})-, or

25 J is a bond, V is a bond, Q is -C(R^{7a})₂-, and T is -C(R^{7b})₂-, or

J is a bond, V is a bond, Q is -C(R^{7a})=, T is =C(R^{7b})-, where the atoms to which R^{7a} and R^{7b} are attached join to form a benzene, pyridine, or diazine ring, or

30 J is a bond, V is C(R⁶)₂, Q is -C(R^{7a})=, T is =C(R^{7b})-, and the atoms to which R^{7a} and R^{7b} are attached join to form a benzene, or pyridine ring, or

35 J is O, V is a bond, Q is -C(R^{7a})=, T is =C(R^{7b})-, and the atoms to which R^{7a} and R^{7b} are attached are joined together to form a benzene, or pyridine ring,

or Z is Z2 and:

G-L is N, Q is $-C(R^{7a})_2-$, and T is $-C(R^{7b})_2-$, or

5

G-L is N, Q is $-C(R^{7a})=$ and T is $=C(R^{7b})-$, or

G-L is N, Q is $-N=$, and T is $=C(R^{7b})-$, or

10

G-L is N, Q is $-C(R^{7a})_2-$, and T is $-C(O)-$, or

G-L is $C=C(R^6)$, Q is $-C(R^{7a})=$ and T is $=C(R^{7b})-$, or

G-L is $C=C(R^6)$, Q is $-C(R^{7a})=$ and T is $=N-$, or

15

G-L is $C=C(R^6)$, Q is $-N=$ and T is $=C(R^{7b})-$, or

G-L is $C=N$, Q is $-C(R^{7a})=$ and T is $=C(R^{7b})-$, or

20

G-L is N, Q is $-C(R^{7a})=$, and T is $=C(R^{7b})-$, and the atoms to which R^{7a} and R^{7b} are attached join to form a benzene, pyridine, or diazine ring, or

G-L is $N-C(R^6)_2$, Q is $-C(R^{7a})=$, and T is $=C(R^{7b})-$, and the atoms to which R^{7a} and R^{7b} are attached join to form a benzene, or pyridine ring, or

25

G-J is $C=N$, Q is $-C(R^{7a})=$, and T is $=C(R^{7b})-$, and the atoms to which R^{7a} and R^{7b} are attached join to form a benzene ring, or

G-L is $C=C(R^6)$, Q is $-C(R^{7a})=$, and T is $=C(R^{7b})-$, and the atoms to which R^{7a} and R^{7b} are attached join to form a benzene ring, or

30

G-L is $N-C(R^6)_2-C(R^6)_2$, Q is $-C(R^{7a})=$, and T is $=C(R^{7b})-$, and the atoms to which R^{7a} and R^{7b} are attached join to form a benzene ring;

35 R^3 is independently selected from H, substituted or unsubstituted C_1-C_3 alkyl, F, CN and CO_2R^4 ;

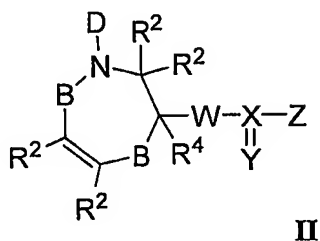
R^{7a} and R^{7b} are each independently selected from R^2 , where R^{7a} and R^{7b} and the atom or atoms to which they are attached optionally join to form a ring selected from C₃-6cycloalkyl, aryl, heterocycle, and heteroaryl which is unsubstituted or substituted with 1-10 substituents each each independently selected from R^6 ;

- 5 p is 0 to $2q+1$, for a substituent with q carbons
 m is 0 to 2;
 s is 1 to 3;

and pharmaceutically acceptable salts and individual stereoisomers thereof.

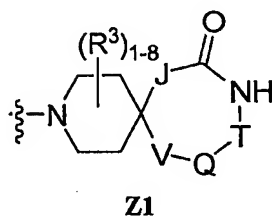
10

7. A compound of the Formula II:



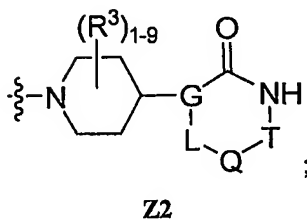
5 wherein:

Z is selected from:



10

and



15

B is $(C(R^2)_2)_n$:

R^1 is independently selected from:

20 1) H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, and heterocycle, unsubstituted or substituted with one or more substituents each independently selected from:

25 a) C₁-C₆ alkyl,
b) C₃-C₆ cycloalkyl,

- 5
- c) aryl, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
- d) heteroaryl, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
- e) heterocycle, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
- f) $(F)_p C_{1-3}$ alkyl,
- g) halogen,
- h) OR^4 .
- 10 i) $O(CH_2)_s OR^4$,
- j) CO_2R^4 .
- k) $(CO)NR^{10}R^{11}$,
- l) $O(CO)NR^{10}R^{11}$,
- m) $N(R^4)(CO)NR^{10}R^{11}$,
- 15 n) $N(R^{10})(CO)R^{11}$,
- o) $N(R^{10})(CO)OR^{11}$,
- p) $SO_2NR^{10}R^{11}$,
- q) $N(R^{10})SO_2R^{11}$,
- r) $S(O)_mR^{10}$,
- 20 s) CN,
- t) $NR^{10}R^{11}$,
- u) $N(R^{10})(CO)NR^4R^{11}$, and,
- v) $O(CO)R^4$, and
- 25 2) aryl or heteroaryl, unsubstituted or substituted with one or more substituents each independently selected from:
- a) C_{1-6} alkyl,
- b) C_{3-6} cycloalkyl,
- 30 c) aryl, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
- d) heteroaryl, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
- e) heterocycle, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
- 35

- 5
- f) $(F)_p C_{1-3}$ alkyl,
 - g) halogen,
 - h) OR^4 ,
 - i) $O(CH_2)_5 OR^4$,
 - j) $CO_2 R^4$,
 - k) $(CO)NR^{10}R^{11}$,
 - l) $O(CO)NR^{10}R^{11}$,
 - m) $N(R^4)(CO)NR^{10}R^{11}$,
 - n) $N(R^{10})(CO)R^{11}$,
 - 10 o) $N(R^{10})(CO)OR^{11}$,
 - p) $SO_2 NR^{10}R^{11}$,
 - q) $N(R^{10}) SO_2 R^{11}$,
 - r) $S(O)_m R^{10}$,
 - s) CN,
 - 15 z) $NR^{10}R^{11}$,
 - aa) $N(R^{10})(CO)NR^4 R^{11}$, and
 - bb) $O(CO)R^4$;

R^2 is independently selected from:

- 20
- 1) H , C_0 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl and heterocycle, unsubstituted or substituted with one or more substituents each independently selected from:
- 25
- a) C_{1-6} alkyl,
 - b) C_{3-6} cycloalkyl,
 - c) aryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4 ,
 - d) heteroaryl, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
 - 30 e) heterocycle, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
 - f) $(F)_p C_{1-3}$ alkyl,
 - g) halogen,
 - 35 h) OR^4 .

- i) $O(CH_2)_sOR^4$,
 j) CO_2R^4 ,
 k) $(CO)NR^{10}R^{11}$,
 l) $O(CO)NR^{10}R^{11}$,
 5 m) $N(R^4)(CO)NR^{10}R^{11}$,
 n) $N(R^{10})(CO)R^{11}$,
 o) $N(R^{10})(CO)OR^{11}$,
 p) $SO_2NR^{10}R^{11}$,
 q) $N(R^{10})SO_2R^{11}$,
 10 r) $S(O)_mR^{10}$,
 s) CN ,
 t) $NR^{10}R^{11}$,
 u) $N(R^{10})(CO)NR^4R^{11}$, and,
 v) $O(CO)R^4$, and
 15
- 2) aryl or heteroaryl, unsubstituted or substituted with one or more substituents each independently selected from:
- a) C_{1-6} alkyl,
 20 b) C_{3-6} cycloalkyl,
 c) aryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R^4 ,
 d) heteroaryl, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
 25 e) heterocycle, unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ,
 f) $(F)_pC_{1-3}$ alkyl,
 g) halogen,
 h) OR^4 ,
 30 i) $O(CH_2)_sOR^4$,
 j) CO_2R^4 ,
 k) $(CO)NR^{10}R^{11}$,
 l) $O(CO)NR^{10}R^{11}$,
 m) $N(R^4)(CO)NR^{10}R^{11}$,
 35 n) $N(R^{10})(CO)R^{11}$,

- o) $N(R^{10})(CO)OR^{11}$,
- p) $SO_2NR^{10}R^{11}$,
- q) $N(R^{10})SO_2R^{11}$,
- r) $S(O)_mR^{10}$,
- 5 s) CN ,
- t) $NR^{10}R^{11}$,
- u) $N(R^{10})(CO)NR^4R^{11}$, and
- v) $O(CO)R^4$,

10 where any two independent R^2 on the same or adjacent atoms optionally join to form a ring selected from cyclobutyl, cyclopentenyl, cyclopentyl, cyclohexenyl, cyclohexyl, phenyl, naphthyl, thienyl, thiazolyl, thiazoliny, oxazolyl, oxazoliny, imidazolyl, imidazoliny, imidazolidiny, pyridyl, pyrimidyl, pyrazinyl, pyrrolyl, pyrroliny, morpholiny, thiomorpholine, thiomorpholine S-oxide, thiomorpholine S-dioxide, azetidiny, pyrrolidiny, piperidiny, 15 tetrahydrofuranyl, tetrahydropyranyl, tetrahydropyridyl, furanyl, dihydrofuranyl, dihydropyranyl and piperaziny;

R^{10} and R^{11} are each independently selected from: H, C_{1-6} alkyl, $(F)_pC_{1-6}$ alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl, and benzyl, unsubstituted or substituted with halogen, hydroxy or C_1-C_6 alkoxy, where R^{10} 20 and R^{11} optionally join to form a ring selected from: azetidiny, pyrrolidiny, piperidiny, piperaziny, and morpholiny, which is ring is unsubstituted or substituted with 1-5 substituents each independently selected from R^4 ;

R^4 is independently selected from: H, C_{1-6} alkyl, $(F)_pC_{1-6}$ alkyl, C_{3-6} cycloalkyl, aryl, heteroaryl and 25 benzyl, unsubstituted or substituted with halogen, hydroxy or C_1-C_6 alkoxy;

W is O, NR^4 or $C(R^4)_2$;

X is C or S;

30 Y is O, $(R^4)_2$, NCN, NSO_2CH_3 or $NCONH_2$, or Y is O_2 when X is S;

R^6 is independently selected from H and:

35 a) C_{1-6} alkyl,

- 5
- b) C₃₋₆ cycloalkyl,
- c) aryl, unsubstituted or substituted with 1-5 substituents where the substituents are independently selected from R⁴,
- d) heteroaryl, unsubstituted or substituted with 1-5 substituents each independently selected from R⁴,
- e) heterocycle, unsubstituted or substituted with 1-5 substituents each independently selected from R⁴,
- f) (F)_pC₁₋₃ alkyl,
- g) halogen,
- 10 h) OR⁴.
- i) O(CH₂)₅OR⁴,
- j) CO₂R⁴.
- k) (CO)NR¹⁰R¹¹,
- l) O(CO)NR¹⁰R¹¹,
- 15 m) N(R⁴)(CO)NR¹⁰R¹¹,
- n) N(R¹⁰)(CO)R¹¹,
- o) N(R¹⁰)(CO)OR¹¹,
- p) SO₂NR¹⁰R¹¹,
- q) N(R¹⁰)SO₂R¹¹,
- 20 r) S(O)_mR¹⁰,
- s) CN,
- t) NR¹⁰R¹¹,
- u) N(R¹⁰)(CO)NR⁴R¹¹, and
- v) O(CO)R⁴;

25

J is a bond, C(R⁶)₂, O or NR⁶;

V is selected from a bond, C(R⁶)₂, O, S(O)_m, NR⁶, C(R⁶)₂-C(R⁶)₂, C(R⁶)=C(R⁶), C(R⁶)₂-N(R⁶), C(R⁶)=N, N(R⁶)-C(R⁶)₂, N=C(R⁶), and N(R⁶)-N(R⁶);

30

G-L is selected from: N, N-C(R⁶)₂, C=C(R⁶), C=N, C(R⁶), C(R⁶)-C(R⁶)₂, C(R⁶)-C(R⁶)₂-C(R⁶)₂, C=C(R⁶)-C(R⁶)₂, C(R⁶)-C(R⁶)=C(R⁶), C(R⁶)-C(R⁶)₂-N(R⁶), C=C(R⁶)-N(R⁶), C(R⁶)-C(R⁶)=N, C(R⁶)-N(R⁶)-C(R⁶)₂, C=N-C(R⁶)₂, C(R⁶)-N=C(R⁶), C(R⁶)-N(R⁶)-N(R⁶), C=N-N(R⁶), N-C(R⁶)₂-C(R⁶)₂, N-C(R⁶)=C(R⁶), N-C(R⁶)₂-N(R⁶), N-C(R⁶)=N, N-N(R⁶)-C(R⁶)₂ and N-N=C(R⁶);

35

Q is selected from:

- (1) $=C(R^{7a})-$,
- (2) $-C(R^{7a})_2-$,
- (3) $-C(=O)-$,
- 5 (4) $-S(O)_m-$,
- (5) $=N-$, and
- (6) $-N(R^{7a})-$;

T is selected from:

- 10 (1) $=C(R^{7b})-$,
- (2) $-C(R^{7b})_2-$,
- (3) $-C(=O)-$,
- (4) $-S(O)_m-$,
- (5) $=N-$, and
- 15 (6) $-N(R^{7b})-$;

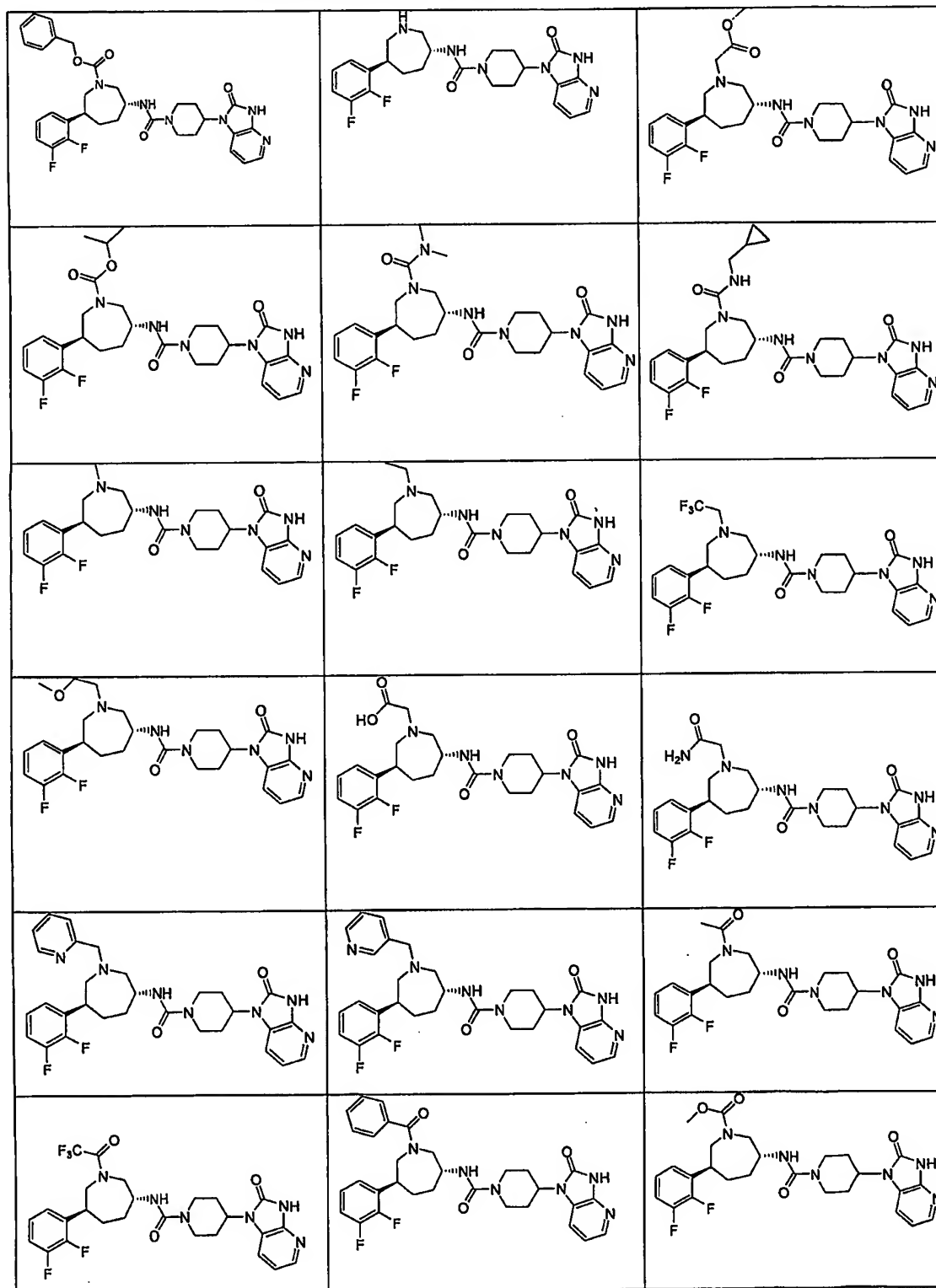
R^3 is independently selected from H, substituted or unsubstituted C_1 - C_3 alkyl, F, CN and CO_2R^4 ;

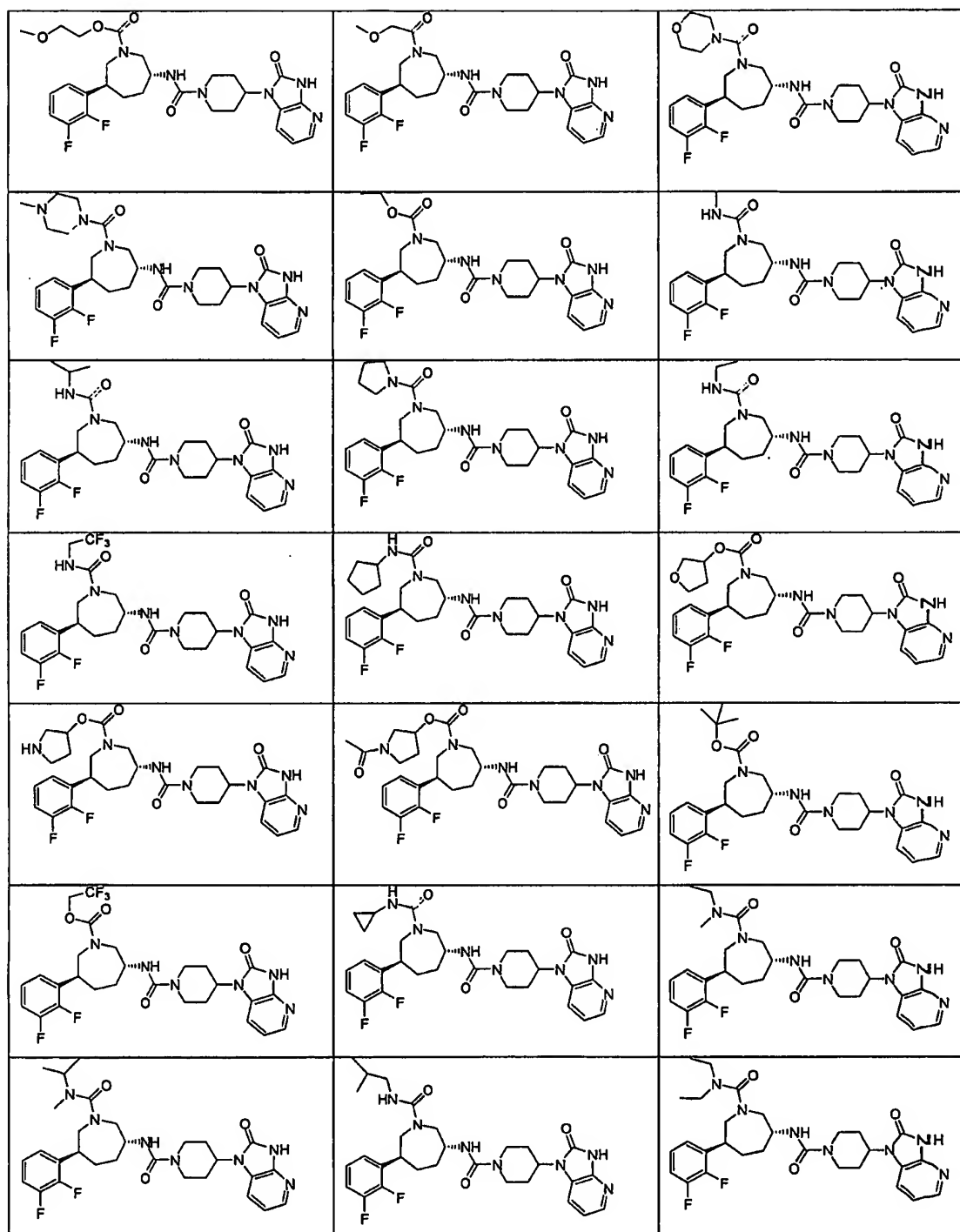
R^{7a} and R^{7b} are each independently selected from R^2 , where R^{7a} and R^{7b} and the atom or atoms to which they are attached optionally join to form a ring selected from C_3 -6 cycloalkyl, aryl, heterocycle, and heteroaryl, which ring is unsubstituted or substituted with 1-10 substituents each independently selected from R^6 ;

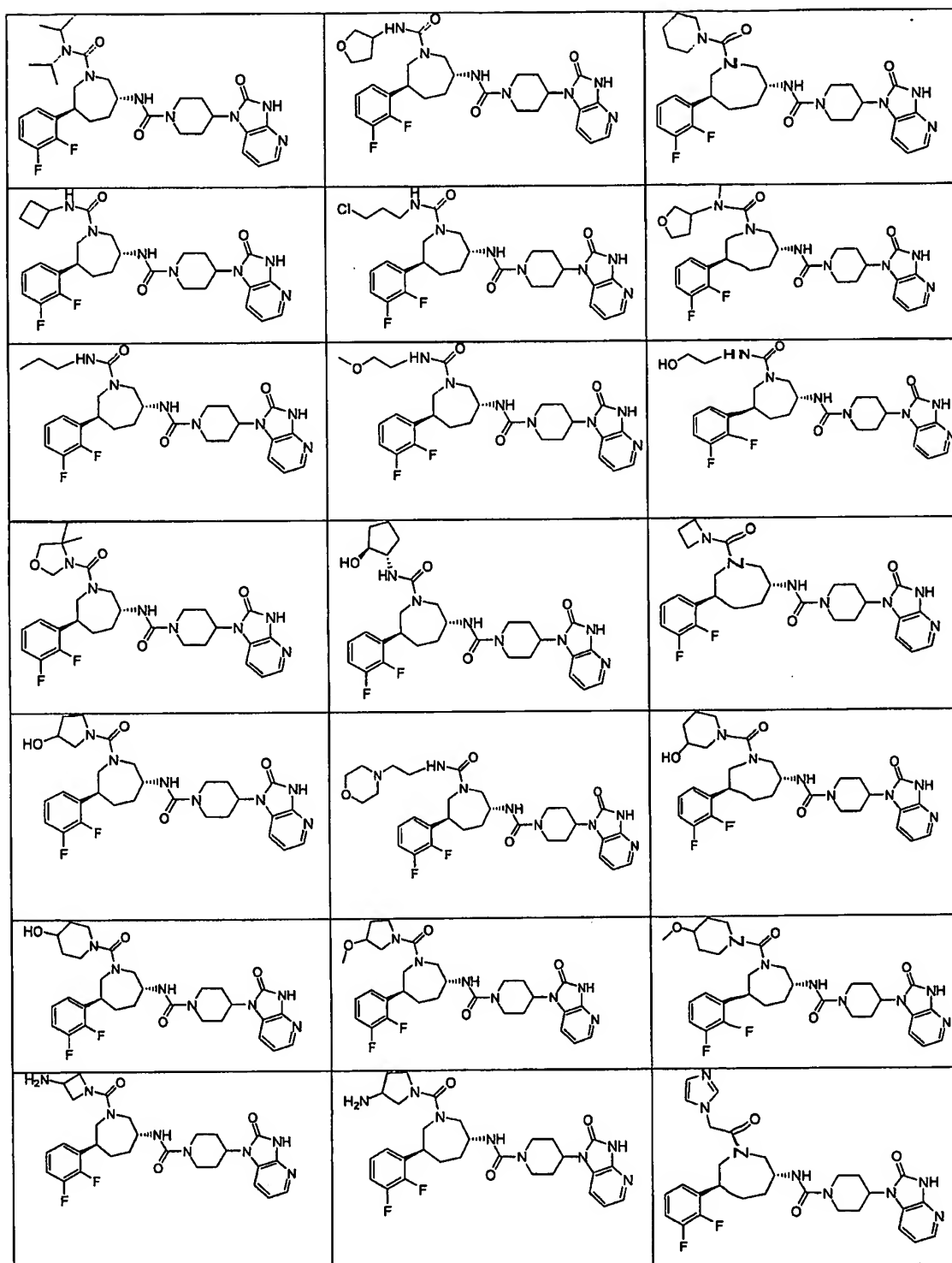
p is 0 to $2q+1$, for a substituent with q carbons;
 m is 0, 1 or 2;
 n is 0 or 1;
 25 s is 1, 2 or 3;

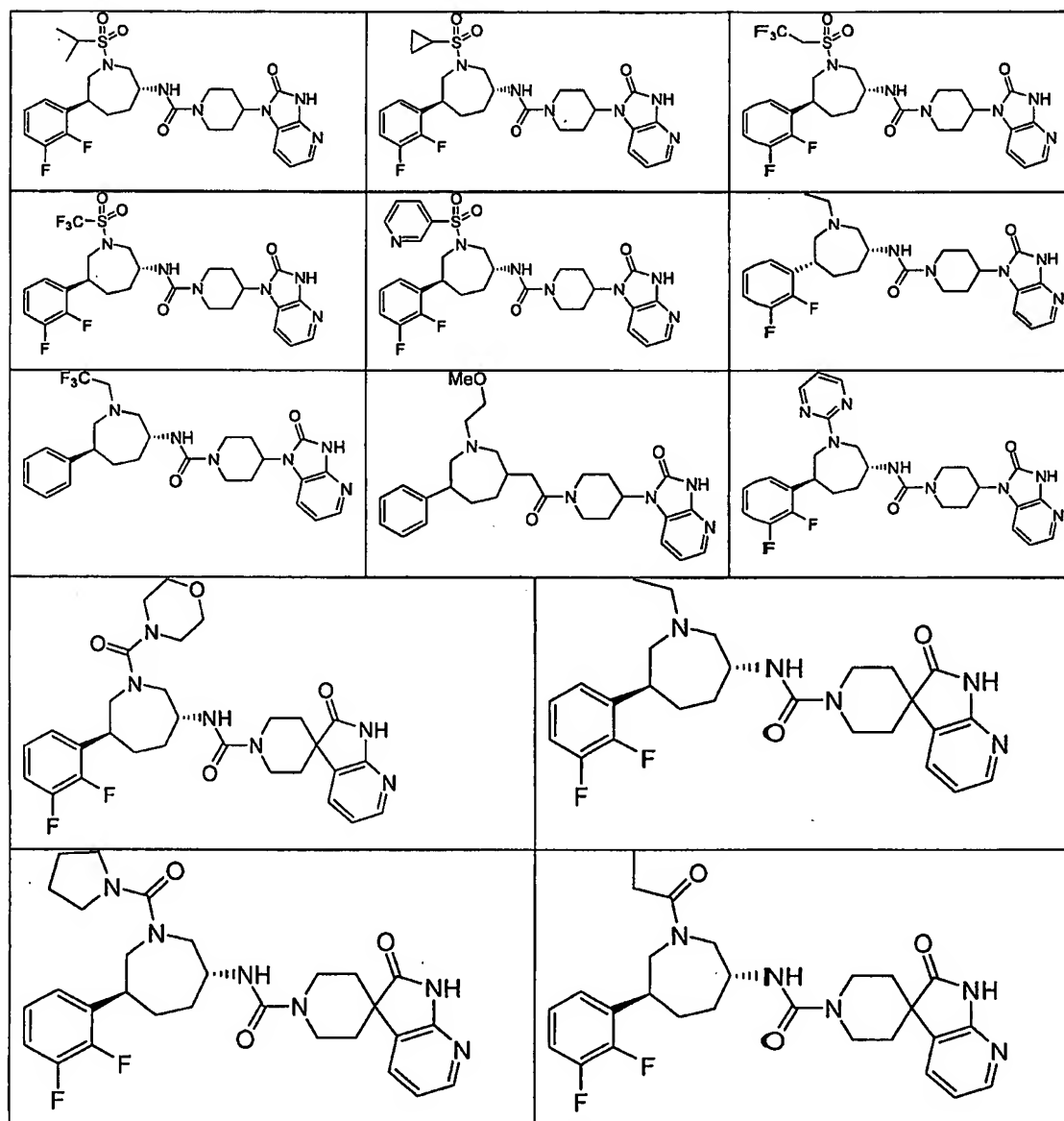
and pharmaceutically acceptable salts and individual diastereomers thereof.

8. A compound selected from:









9. A pharmaceutical composition which comprises an inert carrier and the compound of Claim 1.

5 10. A method for antagonism of CGRP receptor activity in a mammal which comprises the administration of an effective amount of the compound of Claim 1.

11. A method for treating, controlling, ameliorating or reducing the risk of headache, migraine or cluster headache in a mammalian patient in need of such which comprises administering to the patient a therapeutically effective amount of the compound of Claim 1.